NEUROIMAGING STUDY OF THE NEUROCOGNITIVE AND PSYCHOSOCIAL FUNCTIONING OF SURVIVORS OF PEDIATRIC BRAIN TUMORS

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Psychology

December, 2012

Nashville, Tennessee

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To my amazing parents, Mike and Kathy –

I couldn’t have done it without you.

ACKNOWLEDGEMENTS

This work would not have been possible without the dedication and guidance of my advisor, Dr. Bruce Compas, who has provided me not only with the opportunity to do innovative research, but also support and mentorship to develop both as a professional and a person. I would also like to thank the other students in my research lab for whose support and encouragement I am eternally grateful, and the staff at the Vanderbilt University Institute for Imaging Science for their commitment to my training and unending patience. This work was supported by the generosity of Patricia and Rodes Hart, and the Justin and Valere Potter Foundation, and the dedication of the families and children who participated. Finally, I am grateful for the support of my family and friends who have been my guides and role models, providing me with unending love and inspiration to move forward.

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CHAPTER I

Introduction

Pediatric brain tumors are the most common solid tumor diagnosis of childhood, and malignant brain tumors are the second most common cancer diagnosis under the age of 20 (Mulhern & Butler, 2004; Sklar, 2002). This heterogeneous set of diagnoses occurs at an incidence rate of approximately 4.8 cases per 100,000 children per year, and it is estimated that 4,150 new cases of childhood primary non-malignant and malignant brain and central nervous system (CNS) tumors are expected to be diagnosed in the United States in 2011 (Central Brain Tumor Registry of the United States; CBTRUS, 2011). Greater than 70% of these diagnoses are expected in children less than 15 years of age. Despite being the second leading cause of death by disease in children, the overall 5-year survival rate following diagnosis of a primary malignant brain and CNS tumor for children under the age of 20 reached 72.5% by 2007 (CBTRUS, 2011). Many of the improvements in survival are largely due to clinical trials and subsequent modifications in treatment protocols involving a combination of surgery, radiation therapy, and/or chemotherapy (Gottardo & Gajjar, 2008; Partap & Fisher, 2007).

As survival rates have risen, increased attention has been given to late effects experienced by survivors of brain tumors in childhood. A range of late effects have been identified, including problems with endocrine function, cardiac impairment, and physical limitations (Ness & Gurney, 2007). Additionally, survivors often experience significant neurological, neurocognitive, and psychosocial late effects, resulting from a combination

of the effects of the tumor itself and its treatment (Panigrahy & Bluml, 2009). Foremost among documented late effects are neurocognitive late effects, including possible long-term disruptions in brain development, cognitive function, and later school and work performance and social-emotional functioning. Neurocognitive effects may occur as a consequence of the extent and location of a tumor, surgery, radiation and chemotherapy, and complications as a result of treatment (e.g., Glauser & Packer, 1991; Mulhern, Hancock, Fairclough, & Kun, 1992). Psychosocial difficulties have also been consistently documented in survivors, with disruptions in social functioning being the most common (e.g., Mabbott et al., 2005; Schultz et al., 2007; Vannatta, Gartstein, Short, & Noll, 1998).

Before describing the current study, I first provide a brief summary of the treatment of pediatric brain tumors. This is followed by a description of the nature, extent, and severity of documented neurocognitive and psychosocial late effects in survivors of pediatric brain tumors and a conceptualization of the interactions between these domains of deficit. Next, I provide an overview of the current research study aimed at examining the associations between neurocognitive and social deficits in children treated for pediatric brain tumor including study hypotheses. Finally, the methods and results of the study are presented.

Pediatric Brain Tumors: Disease Overview

Although the overall survival rate for pediatric brain tumors has reached 72.5% (CBTRUS, 2011), this overall statistic may be misleading, as incidence rates, treatment modalities, and survival rates vary by tumor location, type, and staging. Over 50% of

pediatric brain tumors arise from the posterior fossa, which includes the cerebellum, brainstem, and fourth ventricle, and the remaining tumors arise from the supratentorial and ventricular regions (Panigrahy & Bluml, 2009). Common posterior fossa/infratentorial tumors include pediatric medulloblastomas, cerebellar astrocytomas, gliomas, and ependymomas. The most common histologies of hemispheric/supratentorial tumors include supratentorial gliomas, craniopharyngiomas, germ cell tumors, choroid plexus tumors, and pineoblastomas.

Treatment approaches for pediatric brain tumors depend on a variety of factors. Surgical resection of the tumor remains the therapeutic mainstay, providing both alleviation of the intracranial tumor burden and a histological diagnosis (Ullrich, 2009). The extent of resection prior to the onset of secondary treatment modalities is highly prognostic, with better outcomes expected in children for whom complete resection occurred (Merchant, Pollack, & Loeffler, 2010). Improvements in surgical approaches, including image-guided surgical techniques and intraoperative imaging have resulted in greater safety and ease of tumor resection (Ullrich, 2009). For some patients, surgical resection and radiographic follow-up may be the only therapy needed; for example, juvenile pilocytic astrocytomas, the most common childhood glioma, are highly localized. Treatment of these low-grade tumors is often limited to maximal surgical resection, and survival rates exceed 90% (CBTRUS, 2011). In some cases, however, surgical resection is impossible due to the location of the tumor relative to essential brain structures. Optic pathway gliomas, for example, are rarely able to be resected due to the proximity of tumors to the optic nerve and the associated risk for vision loss (St. Jude Children's Research Hospital, 2009). In other cases, complete surgical resection is not

possible, or the degree of malignancy is such that additional treatment is necessary to improve survival.

Secondary treatment approaches often involve cranio-spinal irradiation, adjuvant multiagent chemotherapy, or both. Radiation may be focal or may cover the entire brain and spine, depending on the extent to which the tumor has spread (National Cancer Institute, 2008). Although radiation has been associated with increases in survival rates for some diagnoses, significant late effects have been observed in long-term survivors, particularly for young children. Therefore alternatives to this treatment approach have recently been explored (Merchant et al., 2010). In "low-risk" cases, use of radiation treatment may be eliminated all together, and for most patients, dosage of radiation may be reduced by the addition of chemotherapy to treatment protocols. This practice has been adopted most significantly for children diagnosed prior to age 3, as radiation-associated late-effects are most pronounced for survivors diagnosed at an early age. However, use of chemotherapy to avoid or delay use of radiation in young children diagnosed with highly aggressive tumors remains controversial, as survival rates for these children fall below those of older children (Merchant et al., 2010). Presently, age at diagnosis and staging are the overriding factors in treatment protocol selection. However, current research in this area focuses on increasing the specificity of risk-adapted therapy through the better identification of histopathological and molecular predictors of outcome (Merchant et al., 2010).

Decisions about the most appropriate treatment approach for a pediatric brain tumor must take into consideration the associated late effects of a given modality. Risks associated with cranio-spinal irradiation therapy, for example, range from insults to

motor, sensory, coordination, hearing, and visual systems, to significant endocrine dysfunction, to neurocognitive deficits. These effects are magnified in children diagnosed and treated at a younger age (Merchant et al., 2010). For example, one study found that survivors ages 3-7 years treated between with a cranio-spinal axis dose of 3600 cGy of radiation experienced a 20- to 30-point decline in IQ (Packer, Meadows, Rorke, Goldwein, & D'Angio, 1987). Balancing the competing demands of treatment success and reduction of significant and functionally debilitating late-effects is a priority in the field, and accurate and systematic documentation of both epidemiologic and functional outcome data is essential.

Late Effects of Pediatric Brain Tumors

As noted above, as the survival rates for pediatric brain tumors have risen, researchers have paid increased attention to the long-term sequelae of diagnoses and treatment. Recently, two of the most frequently examined types of late effects are neurocognitive deficits and difficulties in psychosocial functioning in survivors of pediatric brain tumor.

Neurocognitive deficits.

Research has emerged examining long-term deficits in neurocognitive function following diagnosis and treatment for pediatric brain tumors, and the early studies in this field reviewed by Glauser and Packer (1991) identified some form of cognitive deficit in at least one domain in 40% to 100% of survivors of pediatric brain tumors. Neurocognitive deficits have been found in a variety of domains, including overall intelligence, executive function, memory, and academic achievement. Research has

reported small to large deficits in most measures of global intelligence, which appear to emerge shortly after treatment ends, and functioning has been found to progressively decline over the following several years (e.g., Mulhern & Butler, 2004; Poggi et al., 2005). Childhood brain tumor survivors have been found to display poor performance on measures of global executive function, working memory, processing speed, and sustained attention, which are related to problems in broader areas intellectual and academic functioning due to difficulties in the acquisition and storage of new knowledge (Mulhern & Butler, 2004).

Given this wide range of deficits found in individual studies, the need is evident for quantification of the magnitude and scope of deficits, and the factors by which they vary. A recent meta-analysis of the neurocognitive deficits in survivors of pediatric brain tumors indicated that children treated for brain tumors exhibit pervasive and substantial deficits along a range of broad and specific neurocognitive domains, including overall cognitive functioning, academic achievement, attention, psychomotor and visual-spatial skill, verbal memory, and language (Robinson, Kuttesch, et al., 2010). Overall, the magnitude of the effects across all domains ranged from small to large in size (g = -.45 to -1.43) with a large mean overall effect size of g = -.91.

One especially important domain of neurocognitive implicated in studies of deficits in survivors of pediatric brain tumors is executive function. Throughout adolescence, these higher order cognitive processes become increasingly important as maturation of the frontal lobes allows children to begin to better integrate complex information and regulate emotions (e.g., Lezak, Howieson, & Loring, 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna & Sweeney, 2004). These processes are

essential factors in the ability to problem solve, engage in goal-directed behavior, and maintain stable interpersonal relationships (Lezak et al., 2004). Children with brain tumors primarily display poor performance on measures of global executive function, working memory, and sustained attention (Ullrich, 2009), which are related to problems in broader areas of intellectual and academic functioning due to difficulties in the acquisition and storage of new knowledge (e.g., Mulhern & Butler, 2004; Mulhern et al., 2004).

The extent to which deficits in overall neurocognitive functioning, and executive function in particular, are associated with other documented areas of deficits in survivors is largely unknown, and further research is needed. Key executive functions, including working memory and response inhibition, have been linked to deficits in social information processing in other populations, including the ability to engage in distinct, problem-solving steps that are implemented when children are faced with social situations in children with traumatic brain injury (Yeates et al., 2007). However, research on the associations between executive function, social competency, and outcomes in survivors of pediatric brain tumors has only recently begun to emerge, and neurobiological underpinnings of these associations have yet to be examined.

Social functioning.

Social difficulties are a consistently reported problem experienced by survivors of pediatric brain tumors (e.g., Fuemmeler, Elkin, & Mullins, 2002; Schulte & Barrera, 2010), and are more apparent for survivors of brain tumors than survivors of non-CNS cancers (e.g., Schultz et al., 2007; Turner, Rey-Casserly, Liptak, & Chordas, 2009). A report from the Childhood Cancer Survivor Study (CCSS), the largest multi-institutional

study of long-term effects of childhood cancer, indicated that survivors of pediatric brain tumors were at 2.6 times greater risk of demonstrating increased antisocial behaviors as compared to healthy children, and their risk of demonstrating diminished social competence was nearly twice that of children with no history of cancer (Schultz et al., 2007).

In their recent review of studies assessing the social competence of survivors of pediatric brain tumors, Schulte and Barrera (2010) reviewed and synthesized the findings of 20 articles published between 2000 and 2009. Overall, studies consistently found that survivors experience impaired social adjustment following treatment, with individual studies documenting deficits relative to siblings (e.g., Schultz et al., 2007), population norms (e.g., Aarsen et al., 2006), healthy controls (e.g., Palmer, Meeske, Katz, Burwinkle, & Varni, 2007), children with other types of chronic illness (e.g., juvenile rheumatoid arthritis; Bonner et al., 2008), and survivors of acute lymphocytic leukemia (e.g., Meeske, Katz, Palmer, Burwinkle, & Varni, 2004)..

Research has found that children treated for pediatric brain tumors have poor social skills and peer relationship problems in school, in addition to academic difficulties (Boydell, Stasiulis, Greenberg, Greenberg, & Spiegler, 2008). When compared to children with juvenile rheumatoid arthritis, survivors of pediatric brain tumors were rated by parents as having more problematic social behaviors, deficits in nonverbal social behaviors, and more social problems overall, after controlling for IQ (Bonner et al., 2008). In the only known study examining the neural bases of social deficits in survivors, researchers found that survivors performed more poorly on tasks of social facial expression recognition, suggesting potential difficulties distinguishing nonverbal

social cues (Bonner et al., 2008). This has broad implications, as processing nonverbal social information during interpersonal interactions becomes increasingly important throughout adolescence (Bonner et al., 2008).

Mabbott and colleagues (2005) found that survivors of posterior fossa tumors experienced increased symptoms of social problems, particularly in cases where treatment included cranial radiation therapy. Growth curve analysis indicated that these deficits in social functioning increased significantly over time, based on both parents' and teachers' report (Mabbott et al., 2005). Survivors have also been found to report poorer quality of life and greater difficulties in the area of social functioning as compared to survivors of other cancers (e.g., Zebrack & Chesler, 2002). In addition, they have been described by parents as less socially competent as compared to healthy children or children with non-CNS malignancies (e.g., Bonner et al., 2008; Carpentieri, Mulhern, Douglas, Hanna, & Fairclough, 1993; Fossen, Abrahamsen, & Storm-Mathisen, 1998; Poggi et al., 2005; Radcliffe, Bennett, Kazak, Foley, & Phillips, 1996).

According to their peers, children who have been treated for a brain tumor are perceived as isolated and withdrawn, and are significantly less likely to be endorsed as a best friend than healthy children (Vannatta et al., 1998). Further, survivors perceive themselves as being significantly more isolated than their peers (Vannatta et al., 1998). When asked to rate themselves on several aspects of psychosocial functioning, survivors perceived themselves as less skilled in the areas of athletics, academics, and social domains (Gerhardt et al., 2008). These survivors also reported greater loneliness and were rated by parents as having more symptoms of internalizing disorders (Gerhardt et al., 2008).

Social deficits may emerge in survivors of pediatric brain tumors for a number of reasons. Researchers have postulated that conditions affecting the CNS may place children at increased risk for problems in social functioning due to cognitive impairments impacting social understanding, peer stigmatization due to visual manifestations (e.g., scars, mobility problems), or reduced opportunities for peer interaction during hospitalization and recovery (Nassau & Drotar, 1997). Children treated for pediatric brain tumors, therefore, may be at particular risk due to the impact of treatment on their physical appearance and mobility, ability to attend school or participate in a mainstream classroom, and ability to process social information due to deficits in neurocognitive domains.

Emotional functioning.

In addition to deficits in social functioning, survivors of pediatric brain tumors are at risk for psychosocial distress, including symptoms of anxiety and depression (Fuemmeler et al., 2002; Rey-Casserly & Parsons, 2006). In their review of studies of the emotional adjustment of survivors, Fuemmeler and colleagues (2002) identified eight studies published between 1979 and 1997, reporting rates of internalizing symptoms (e.g., anxiety, depression) in children treated for brain tumors. Results of these studies were mixed, with some indicating survivors were more likely to experience internalizing symptoms, and others suggesting survivors' were no more likely than healthy children to experience these symptoms.

An early study by Hirsch, Renier, Czernichow, Benveniste, & Pierre-Kahn, (1979) indicated that survivors of pediatric brain tumors were at increased risk of "emotional problems," with 93% of survivors endorsing symptoms. Although the term

"emotional problems" was not operationally defined in the article, these authors documented difficulties in the areas of instability, slowness, anxiety, inhibition, and negative attitude, which map onto internalizing symptoms (Fuemmeler et al., 2002). In a follow-up study on this sample of survivors, Hoppe-Hirsch et al. (1990) reported that, of the participants able to be contacted for follow-up assessments, 47% (26 of 55 participants) of this sample continued to experience symptoms 5 years after treatment, and 77% (10 of 13 participants) after 10 years. Similarly, Seaver et al. (1994) found that 44% of survivors experienced clinically-significant symptoms of internalizing based on a structured interview of overall psychological functioning. In contrast, Radcliffe et al. (1996) found that survivors rated themselves as significantly less depressed and less anxious than normative samples, whereas parents and teachers of this sample of survivors rated them as equally as likely as normative samples to experience symptoms of internalizing. Importantly, studies reporting elevated symptoms most often relied on parent reports of internalizing problems, whereas children reported fewer problems. This suggests that multi-informant designs may be beneficial in determining better estimates of these problems in survivors.

Other studies have examined emotional functioning of survivors of pediatric brain tumors relative to other clinical populations or healthy children. A report from the CCSS indicated that brain tumor survivors were twice as likely as healthy siblings to report symptoms of depression and anxiety (Schultz et al., 2007). Mulhern, Carpentieri, Shema, Stone, & Fairclough (1993) examined rates of internalizing symptoms in survivors of pediatric brain tumors versus survivors of cancers outside of the CNS. They found clinically elevated symptoms of internalizing in 30% of the sample of brain tumor

survivors and 20% of the sample of survivors of non-CNS cancers. Although rates of internalizing in this study did not differ between clinical samples, rates for each sample statistically exceeded the expected rate of internalizing (7%) based on the general population. In a study comparing psychological adjustment problems of brain tumor survivors relative to children who had survived traumatic brain injuries, Poggi et al. (2005) found evidence of significant psychological disorders in 26.7% of survivors of pediatric brain tumors. The most frequently endorsed symptoms within this sample of survivors included symptoms of internalizing disorders (73.3%), withdrawn behavior (26.7%), and social problems (13.3%).

Overall, the majority of studies on the emotional functioning of survivors of pediatric brain tumors suggest that survivors are at elevated risk for experiencing symptoms of internalizing disorders. However, rates of symptoms or disorders in individual studies suggest that only a subset of survivors experience these difficulties. Although a few studies have considered predictors of psychosocial and emotional functioning (e.g., Carpentieri et al., 1993; Foley, Barakat, Herman-Liu, Radcliffe, & Molloy, 2000; Seaver et al., 1994), further research is warranted.

Coping and emotion regulation.

One possible predictor of the emergence of psychosocial and emotional difficulties in survivors of pediatric brain tumors is the skill with which survivors cope with stress and interpersonal problems, and regulate their emotions. For example, Fuemmeler, Mullins, Van Pelt, Carpentier, and Parkhurst (2005) examined the association between coping strategies and levels of posttraumatic stress symptoms (PTSS) in a group of survivors of childhood cancer, some of whom were treated for

pediatric brain tumors. Results indicated that less use of emotion-focused coping (e.g., distancing, self-controlling, accepting responsibility, escape-avoidance, and positive reappraisal) was associated with increased frequency of PTSS as well as general psychological distress across all participants in this study. However, it is not known whether this pattern holds true specifically for survivors of pediatric brain tumors, and in general, research has yet to consider the ways in which brain tumor survivors cope with stress.

In the present study, coping is conceptualized based on a multidimensional model of coping and stress reactivity (Connor-Smith, Compas, Wadsworth, Thomsen, & Saltzman, 2000). According to this framework, coping includes voluntary responses implemented in stressful situations, and is defined as "conscious, volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances" (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001, p. 89). Several skills outlined in this model rely heavily on self-regulatory skills that depend on the use of complex problem solving and higher order executive function.

Coping responses are divided into dimensions based on orientation towards vs. away from a stressor or one's reactions to the stressor. Coping responses that orient a person toward the stressor are classified as engagement responses, and responses that orient a person away from the stressor are classified as disengagement responses. Engagement responses are further classified as primary control coping strategies or secondary control coping strategies. This model has been validated in multiple studies of children and adolescents (e.g., Compas, Boyer, et al., 2006; Connor-Smith et al., 2000;

Wadsworth, Rieckmann, Benson, & Compas, 2004) and adults (Compas, Beckjord, et al., 2006).

Primary control coping strategies aim to change the stressor or situation itself, and include problem solving, emotional modulation, and emotional expression. In contrast, secondary control coping strategies aim to manipulate or adjust one's own reactions to the stressor, and include strategies like positive thinking, cognitive restructuring, acceptance, and distraction. Disengagement coping responses include avoidance, denial, and wishful thinking. Whereas primary and secondary control coping responses have been found to be associated with lower levels of emotional and behavioral problems in children and adolescents, disengagement responses have been associated with higher levels of emotional and behavioral problems (e.g., Compas, Boyer, et al., 2006; Jaser et al., 2007).

Integration of neurocognitive and psychosocial deficits.

Although research on social, emotional, and neurocognitive functioning clearly suggests that survivors of pediatric brain tumors can experience difficulty in several areas, the associations among these problems remain unclear.

It has been suggested that disturbances in cognitive and neuropsychological functioning resulting from a pediatric brain tumor may result in the onset of psychological and behavioral problems (Poggi et al., 2005), but research documenting this association is still emerging. Nassau and Drotar (1997) hypothesized that children with CNS-related chronic health conditions (e.g., cerebral palsy, epilepsy, spina bifida) may exhibit deficits social functioning as a result of cognitive impairments that hinder their understanding of social cues and social relations. In one study, researchers found

evidence of deficits in overall and specific areas of neurocognitive functioning, and psychosocial functioning, including social deficits (Carey, Barakat, Foley, Gyato, & Phillips, 2001). Further, these researchers found that nonverbal intelligence was marginally associated with parents' reports of children's social skills, such that as nonverbal intelligence increased, so did social functioning.

In a recent study on the cognitive and psychosocial functioning of 76 brain tumor survivors, Poggi and colleagues (2005) found that parent-reported internalizing, social problems, withdrawn behavior, and total problems on the Child Behavior Checklist (CBCL) were associated with lower full scale IQ. When participants were divided into age groups, cognitive deficits were associated with social problems for children under the age of 6 at assessment, but not for older children. Additionally, Holmquist and Scott (2002) examined the associations between treatment effects and behavioral outcome, and found that difficulties in verbal learning accounted for a significant 51% of the variance in social withdrawal, and overall intellectual functioning accounted for a significant 36% of the variance in social problems in survivors. In contrast, Hardy and colleagues (2010) found that, overall, indicators of cognitive functioning were not related to perceived social competency, with the exception of a positive association between survivors' processing speed and perceived competence in athletics (Hardy, Willard, Watral & Bonner, 2010).

Models of social-cognitive development and social information processing suggest that deficits in neurocognitive, social and emotional functioning may share common underlying mechanisms (e.g., Crick & Dodge, 1994; Lemerise & Arsenio, 2000). In their model of social information processing, Crick and Dodge (1994) describe

the roles of a variety of skills in order for processing to occur. These include attending to social cues during interactions, correct interpretation of cues, the generation of potential responses, imagining possible consequences of these responses, and acting on the selected response. Intuitively, deficits in any of the contributing skills may influence a child's ability to process social information in an effective and efficient manner.

More recently, Yeates et al. (2007) provided a conceptual framework for social information processing within the context of childhood brain disorder. Specifically, this model incorporated the fields of social cognitive neuroscience and developmental psychology to examine the social deficits observed in children treated for traumatic brain injury. These researchers theorized that social information processing involves not only the problem solving steps described above (Crick & Dodge, 1994), but also relies on cognitive constructs including executive function and emotion regulation. A person's responses within the context of social interactions, therefore, are dependent upon his or her cognitive/executive functions, social problem solving ability, and emotional functioning.

Several specific cognitive skills have been considered in research on contributing factors to successful social functioning. Research on the cognitive skills necessary for social information processing has examined regulation of attention, working memory, and processing speed. Other research has found that selective attention, perception, memory, and processing speed skills each set limits on what children notice and process about situations (Lemerise & Arsenio, 2000). Access to social groups to increase knowledge of possible outcomes and consequences of behaviors have also been considered as environmental contributors (Crick & Dodge, 1994).

Although the association between neurocognitive function, most importantly executive function, and coping skills in survivors of pediatric brain tumors has yet to be examined, existing research with other populations can serve as a framework for the conceptualization of these associations (Compas, 2006; Compas, Campbell, Robinson, & Rodriguez, 2009). In a review of the association between coping and attention in the context of child health, Compas and Boyer (2001) suggested that the regulatory processes available for an individual to use are constrained by his or her biological, cognitive, social, and emotional development. Several important cognitive abilities, including sustained attention, cognitive flexibility, and metacognition, are necessary for the engagement in coping strategies such as cognitive reappraisal or problem solving. Therefore, it is likely that a survivor experiencing significant neurocognitive late-effects in the area of executive function may be unable to develop beneficial coping skills, and/or use these skills effectively. Because these engagement coping responses have been associated with a more positive outcome, this may leave survivors of pediatric brain tumors more vulnerable to social and emotional difficulties.

Hocking, Barnes, Shaw, Lochman, Madan-Swain, and Saeed (2011) recently examined the associations between executive function, coping, and symptoms of anxiety and depression in a sample of children with functional abdominal pain. Within this sample, significant correlations were found between selective attention (i.e., the ability to identify and attend to the important elements of a stimulus) and use of secondary control coping, indicating that children with abdominal pain who had better selective attention also reported greater use of these coping responses. Additionally, use of secondary control coping was inversely related to anxiety symptoms, such that children who used

more of these coping responses were less likely to report symptoms of anxiety. Examination of the potential mediating role of coping indicated that secondary control coping responses significantly mediated the association between selective attention and anxiety, as well as the association between attentional control and anxiety (Hocking et al., 2011).

One particularly relevant recent study examined the association between neurocognitive functioning, behavioral functioning, and coping in survivors of pediatric acute lymphocytic leukemia (ALL; Campbell et al., 2009). Within the group of survivors of ALL, significant correlations were found between measures of executive function and primary and secondary control coping. Additionally, significant negative associations were found between primary and secondary control coping and behavior problems, as well as between executive function and behavior problems. Examination of the potential mediating role of coping in the association between executive function and behavior problems suggested that secondary control coping significantly mediates the relationship between several specific domains of executive function (i.e., working memory, cognitive flexibility, self-monitoring) and behavior problems in survivors of ALL (Campbell et al. 2009). Although these patterns of association have yet to be examined in survivors of pediatric brain tumors, similarities in late effects profiles highlight a need for consideration of similar processes in this group of survivors.

Neurobiological underpinnings of neurocognitive and psychosocial functioning.

Although research on survivors of pediatric brain tumors has not directly examined the neurobiological underpinnings of neurocognitive deficits and their

contribution to social functioning, it has been suggested that the areas of executive function, coping and emotion regulation, and social cognition may share underlying neurobiological mechanisms (Compas, 2006; Compas et al., 2009; Yeates et al., 2007). The extent to which deficits in these areas manifest at a neurobiological level within children with acute and chronic illnesses is relatively unknown. However, examination of neurobiological networks underlying these skills would provide valuable information toward better understanding of the mechanisms underlying observed deficits.

Executive function skills improve throughout childhood and adolescence, and improvements in these skills have frequently been attributed to maturation of the prefrontal cortex (Gogtay et al., 2004; Tamnes et al., 2010). In particular, lesion studies documenting deficits in executive function in patients with anterior brain injuries have led to the conclusion that the neural substrates of these skills lie in the prefrontal regions alone (Alvarez & Emory, 2006; Collette, Hogge, Salmon, & Van der Linden, 2006). Research has indicated that response selection, decision making, and volitional control of behavior can all be linked to activation in the prefrontal and anterior cingulate cortices (Adolphs, 2001). However, more recent imaging studies have suggested that the neurobiological underpinnings of executive function extend beyond this single region, and likely involve both frontal and parietal regions, as well as their coordination (Tamnes et al., 2010).

Although caution should be taken in applying the findings of neuroimaging studies in adults to children and adolescents due to differences in amount and dispersion of activation (Nagel, Barlett, Schweinsburg, & Tapert, 2005), studies using fMRI have indicated a pattern of prefrontal and parietal activation in both adolescents and adults

during engagement in tasks relying on executive function (e.g., Kwon, Reiss, & Menon, 2002; Nelson et al., 2000). A recent meta-analysis of studies of brain regions activating during a working memory task in adult subjects provides a relevant starting point for future studies (Owen, McMillan, Laird, & Bullmore, 2005). This review synthesized the findings of 24 functional neuroimaging studies using the N-back working memory paradigm, one of the most often employed paradigms for the assessment of working memory in an imaging context. Evidence of robust activation was found in the lateral premotor cortex, dorsal cingulate cortex, medial premotor cortex, dorsolateral and ventrolateral prefrontal cortices, frontal poles, and medial and lateral posterior parietal cortices (Owen et al., 2005). Studies examining activation during the N-back within samples of children and adolescents has similarly identified prefrontal-parietal networks (Nelson et al., 2000; Thomas et al., 1999).

Other studies have examined patterns of blood-oxygenated level dependent (BOLD) signal activation during working memory task completion in pediatric populations. McAllister and colleagues (1999) examined brain activation during N-back task completion in children who had suffered mild traumatic brain injury, relative to a sample of healthy children. Their findings indicated that both survivors of TBI and healthy children recruited similar networks of brain regions to facilitate task completion, including prefrontal and parietal regions. Interestingly, an interaction between group and task difficulty was detected, such that healthy controls showed increases in activation in the right dorsolateral prefrontal and parietal cortices as the task difficulty increased from the 0-back to the 1-back, and minimal additional increases from the 1-back to the 2-back condition. Survivors of TBI, in contrast, showed a slight increase in activation from the

0-back to the 1-back condition, and extensive activation from the 1-back to the 2-back conditions (McAllister et al., 1999). This suggests that although brain injury may not lead to full loss of functioning of a given region, distribution of resources during task completion may vary in clinical populations relative to healthy children.

The field of social cognitive neuroscience provides a platform for the integration of knowledge about brain structure, function, and their unique and shared contribution toward overall social development (Lieberman, 2007; Yeates et al., 2007). Satpute and Lieberman (2006) discuss a dual-process model of social cognition, which distinguishes between automatic and controlled processes of social perception. Relevant to the current study are controlled processes, which rely heavily on executive function. Specifically, the lateral prefrontal cortex, medial temporal lobe, posterior parietal cortex, rostral anterior cingulate cortex, medial prefrontal cortex, and dorsomedial prefrontal cortex have been hypothesized to underlie willful, consciously experienced reactions that involve reflection, serial processing, and mental representation (Satpute & Lieberman, 2006). It is possible, therefore, that individuals with deficits in executive function may struggle with these aspects of social cognition.

Several brain regions have been postulated to play a role in social cognition, as well as affective processes (Satpute & Lieberman, 2006; Yeates et al., 2007). The cingulate cortex, for example, has been associated with emotion processing and social skills including theory of mind, as well as the processing of emotional and cognitive conflict. The orbitofrontal cortex has been found to be related to these social skills as well, and is involved in processes of self-regulation. The medial prefrontal cortex has been linked to emotion regulation, emotional responses to stimuli interpreted as

emotionally arousing, and assessing outcomes that have a reward/punishment component (Yeates et al., 2007). The lateral prefrontal cortex has been associated with effortful and resource-demanding cognitive tasks that require manipulation, reasoning, working memory, or other complex problem-solving skills. Finally, the posterior parietal cortex has been found to activate when tasks require reasoning and working memory processing (Satpute & Lieberman, 2006).

Importantly, several brain regions implicated in studies of social cognition overlap with regions implicated in basic executive function. This overlap suggests that key executive functions, including working memory, are actively engaged when individuals are faced with conflicts with a social component. These overlapping regions include the cingulate cortex, medial and lateral prefrontal cortices, orbitofrontal cortex, and posterior parietal cortex.

Research on the neurobiological underpinnings of coping and emotion regulation has implicated several brain regions as important in these processes. Whereas activation of many of the brain regions identified in the dual-process model of social cognition indicate emotional arousal (e.g., amygdala; Lieberman, 2007; Satpute & Lieberman, 2006), others have been linked to attempts to regulate, modify, or otherwise cope with emotions. The cingulate cortex, for example, has been tied to the processing of emotional information, particularly in the context of conflict. The orbitofrontal cortex has been tied to self-regulation, and the medial frontal cortex has been linked to processes of emotion regulation and outcome monitoring when stimuli contain a socially relevant component (Yeates et al., 2007).

The association between executive function abilities and coping suggests that the

development of good coping skills likely parallels (and is therefore associated with) the development of the prefrontal cortex (Compas, 2006; Compas & Boyer, 2001). Although imaging of the neurobiological bases of specific coping strategies is still in its early stages, a recent study by McRae, Hughes, Chopra, Gabrieli, Gross, and Ochsner (2010) examined the differences in brain activation when participants engaged in distraction versus reappraisal, which both fall under the category of secondary control coping in the framework used in the current study (Connor-Smith et al., 2000). McRae et al. (2010) found that both distraction and reappraisal were related to reduction of activation in the amygdala, left insula, right inferior parietal lobule, and middle temporal gyrus, and to increased activation in the left middle and inferior prefrontal cortices, dorsomedial prefrontal cortex, and dorsal anterior cingulate cortex. Although no known functional neuroimaging studies have been conducted to examine neurobiological processes associated with use of primary control coping or disengagement coping, determining whether similar or distinct networks subserve these subtypes of coping may be useful towards understanding the impact of insult to a particular brain region on one's ability to cope.

In summary, deficits in executive function, social information processing, and subsequently in social relationships are consistently found in survivors of pediatric brain tumors, and research suggests that difficulties in social functioning are among the most often cited problems experienced by these children (Schulte & Barrera, 2010). Although research has strongly supported the presence of social and executive function deficits in survivors, the mechanisms underlying these deficits are not well understood. Possible mechanisms are suggested by research in social cognitive neuroscience that has

implicated several brain regions as playing a role in deficits of this nature, including the anterior cingulate cortex, medial and lateral prefrontal cortices, orbitofrontal cortex, and posterior parietal cortex (e.g., Amodio & Frith, 2005; Mah, Arnold, & Grafman, 2004; Robinson, Livesay, et al., 2010; Yeates et al., 2007). Research to date has largely focused on reports of behavioral data, and utilization of neuroimaging methods to examine the neurological mechanisms underlying evidenced deficits has been limited to studies of survivors' processing of human emotional faces (Bonner et al., 2008) and activation in sensory brain regions (e.g., Zou et al., 2005). Research on the functional underpinnings of these deficits in survivors of pediatric brain tumors is a necessary next step in understanding the predictors of and implications of these deficits.

Current Studies: Rationale and Hypotheses

To advance research in this area, the current research had several goals which were explored in two studies. First, in Study I, we examined executive function during neurocognitive assessment, working memory task performance, and patterns of BOLD signal activation during functional magnetic resonance imaging (fMRI) in child and adolescent survivors of brain tumor and healthy controls in order to examine whether brain tumor survivors demonstrate deficits in these domains relative to age and gender matched healthy children. In Study II, in order to explore the range of deficits experienced by brain tumor survivors, assessment of executive function and patterns of BOLD signal activation during a verbal working memory task was completed in a larger sample of survivors of pediatric brain tumors; further, the associations between BOLD signal activation and measures of psychosocial functioning and coping were explored.

CHAPTER II

Study I

The goals of Study I were to explore differences in executive function abilities in brain tumor survivors, relative to matched healthy control children, using neuropsychological assessment, working memory task performance during fMRI, and BOLD signal activation during fMRI. The following specific hypotheses were tested:

Hypothesis 1. Consistent with literature on late effects of pediatric brain tumor, survivors will exhibit poor performance, relative to healthy controls, on measures of neurocognitive and executive function, including the areas of working memory, processing speed, overall cognitive ability.

Hypothesis 2. Brain tumor survivors will perform more poorly on a verbal working memory task administered during fMRI, relative to healthy controls. Specifically, survivors will demonstrate lower accuracy, and slower reaction times, than healthy children.

Hypothesis 3. Differences in brain activation between brain tumor survivors and healthy controls during a verbal working memory task will be explored. In parallel with findings of a study on survivors of ALL (Robinson, Livesay, et al., 2010), it is expected that brain tumor survivors will show patterns of compensatory activation in specific regions, including the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), as compared to healthy children. This pattern of processing will be manifested in increased

recruitment of oxygenated blood to these brain regions, relative to healthy controls, as task difficulty increases.

Method

Participants.

Seven survivors of pediatric brain tumor (4 girls) and 7 healthy children (4 girls) were included in these analyses. These children constituted a subset of participants in a larger study on neurocognitive functioning of survivors of pediatric brain tumor. Survivors were identified through the Childhood Cancer Survivorship Clinic in the Department of Pediatric Hematology/Oncology, or the Department of Neurology, at Vanderbilt University Monroe Carrel Jr. Children's Hospital. Healthy children were identified through the Vanderbilt University StudyFinder program, and were matched to survivors for age and gender.

Six brain tumor survivors and 6 healthy controls self-identified as Caucasian, and one participant in each group self-identified as African American. Upon enrollment in the study, brain tumor survivors were on average 12.91 years old (SD = 2.96) and healthy controls were 12.95 years old (SD = 2.76). On average, survivors were diagnosed at 6.30 years old (SD = 2.77; range 2.06-10.74 years) with a brain tumor, and were on average 6.60 years post-diagnosis (SD = 3.31; range 2.20-10.60 years). Tumor pathologies included juvenile pilocytic astrocytoma (n = 5), posterior fossa medulloblastoma (n = 1), and left temporal dysembryoplastic neuroepithelial tumor (n = 1). All procedures were approved by the Institutional Review Board, and informed consent and assent were obtained from all participants.

Demographic information for participants can be found in Table 1. Between groups *t*-tests and chi-square analyses were conducted to assess whether group matching was successful. Results indicated that brain tumor survivors and healthy controls were similar in terms of age (t = -0.03, p = .98), gender (X^2 = 0.00, p = 1.00), race (X^2 = 0.00, p = 1.00), primary caregiver's marital status (X^2 = 1.09, p = .58), primary caregiver's level of education (X^2 = 4.48, p = .35), and family income (X^2 = 6.53, p = .37). This suggests that survivors and healthy controls were adequately matched in terms of demographic characteristics.

Table 1
Group Comparisons on Demographic Information[a]

	Survivors (*n = 7)*	Healthy Controls (*n = 7)*	t/χ^2	*p*	Cohen's *d*
Demographics					
Child Age	12.91 (2.96)	12.95 (2.76)	-0.03	.98	-0.01
Child Gender	57.1% Female	57.1% Female	0.00	1.00	
Child Race	85.7% Caucasian	85.7% Caucasian	0.00	1.00	
Parent Marital Status	85.7% Married	71.4% Married	1.09	.58	
Parent Education	4.57 (1.40)	5.71 (0.95)	4.48	.35	
Family Income	6.57 (2.76)	5.71 (2.43)	6.53	.37	
Time Since Diagnosis	6.60 (3.31)	na			

Note. For survivors, a mean parent education of 4.57 corresponds to some post-high school training, and a family income of 6.57 corresponds to an income range of $50,000-$60,000. For healthy controls, a mean parent education of 5.71 corresponds to some college education, and a family income of 5.71 corresponds to an income range of $40,000-$50,000.
[a]Values in parentheses indicate standard deviation.

Procedure.

Parents or caregivers of brain tumor survivors were sent a letter from a physician informing them of the study and providing a contact number to call in order to opt out of

being contacted regarding participation. Approximately two weeks after the letter was sent, families were contacted by the study coordinator to provide more information and assess the family's interest in participating. Healthy controls responded to a study advertisement posted on the Vanderbilt University StudyFinder website. For each family expressing interest, a brief phone screen was conducted to ensure families met inclusion criteria, and study appointments were scheduled for either one full day or two half-days, depending on each family's preference, and study questionnaires and consent/assent forms were mailed to each family's home. Informed consent and assent were obtained from participants and parents in person during study appointments. After a research assistant answered all questions regarding the study, parents and children completed their appointments.

Study participation included a neurocognitive assessment battery completed with a trained graduate student, completion of questionnaire measures, and a neuroimaging session, including structural, functional, functional connectivity, and diffusion tensor imaging. Neurocognitive assessments included measures of overall cognitive functioning, memory, visual-spatial integration, and executive function. Additionally, parents and children completed several questionnaire measures assessing various domains of functioning, including psychosocial, emotional, and behavioral problems, executive function, and coping.

All imaging was conducted on a 3Tesla MR scanner (Philips Medical Systems, The Netherlands) dedicated for research. The general imaging protocol involved acquiring data for anatomic, functional, functional connectivity and diffusion-tensor analysis. These provided measures of brain tissue volume, function, and microstructure

in an exam of 60-70 minutes. After arriving for their neuroimaging appointment, families were taken to a mock scanner room, which included a structure resembling an MRI, and children we encouraged to climb into the scanner to become familiar with the enclosed space. Children were also shown the headset and the response pad that would be attached to each child's dominant hand during the scan. Once children were comfortable with the scanning environment, children were taught how each of the computerized tasks ran and would appear during the scan. Remaining questions were answered and children were taken back to the scanning room where they were placed in the scanner by a certified technician and trained study personnel. In addition to the response pad, a pulse oximeter was attached to participants' non-dominant index finger to record heart rate, and a respiration belt was placed over participants' diaphragm to record respiration rate. Protocols were run via computer in an adjacent room, and task stimuli appeared via rear projector on a screen mounted in the MRI. Participants were able to respond to questions using buttons on the response pad, and they were able to communicate reciprocally with study personnel throughout the scan through headphones and a microphone.

Measures.

Neurocognitive assessment.

At their assessment session, children completed a brief neurocognitive testing battery. Among other measures, children completed 8 subtests of the Wechsler Intelligence Scale for Children –Fourth Edition (WISC-IV; Wechsler, 2003) to measure overall cognitive functioning, including general verbal and nonverbal intelligence, working memory, and processing speed. The Working Memory Index (WMI) is

composed of the Digit Span and Letter-Number Sequencing subtests, and the Processing Speed Index (PSI) is composed of the Coding and Symbol Search subtests. These indices are of particular interest due to the frequently documented deficits in these domains in survivors of pediatric brain tumors (Robinson, Kuttesch, et al., 2010). In these analyses, participants' full-scale IQ (FSIQ), WMI, and PSI were examined. The Wechsler intelligence scales have demonstrated excellent internal consistency (α = .97) and test-retest reliability (r = .93), as well as established convergent and discriminant validity.

***Functional neuroimaging*.**

During their first functional scan, participants completed the N-back task, which is designed to assess working memory. A letter version of the visual N-back task (Barch, Sheline, Csernansky, & Snyder, 2003) has been developed, and involves sequences of uppercase consonants. In the 0-back condition, participants were instructed to respond to a single target (i.e., V). In the 1-back condition, participants were instructed to respond only when the consonant was identical to the one preceding it (e.g., M, M). In the 2-back condition, participants responded only when the consonant was identical to the one presented two trials prior (e.g., M, T, M), and in the 3-back condition, participants responded when the consonant was identical to the one presented three trials prior (e.g., M, T, F, M). Each condition was presented three times in order of increasing difficulty, for a total of 12 blocks. Each block contained 15 consonants, and 3 of these consonants required a response. This task has been used effectively with children in this age group with no adverse effects (Robinson, Livesay, et al., 2010). N-back task performance data were extracted using ePrime software (Psychology Software Tools Inc., Pittsburgh, PA). Accuracy, reaction time, number of omissions, and number of false positive responses

were calculated for each participant at each level of N-back difficulty. Overall accuracy and reaction time total scores across N-back difficulty level were also calculated.

Image acquisition.

Imaging consisted of a 3-plane localizer (5 slices per plane, 22s scan time) from which 33 oblique axial slices (parallel to the AC-PC plane) were prescribed. High resolution 3D anatomical images were acquired using an inversion-prepared spoiling gradient recalled echo sequence (IR-SPGR), with an inversion time T1 of 400ms, a TR of 15ms, minimum TE (3ms), a matrix size 256x256 for a FOV of 256x256x270mm^3 with near isotropic resolution, for use in volumetric analysis. All functional images were acquired with a gradient echo EPI pulse sequence, with TE 30ms (optimized for T2* at 3T), flip angle of 70°, TR 2000ms, 33 slices 3.5mm thick and .35mm skip, and a matrix size of 80x80 (reconstructed to 128x128) sampled at +/-62.5kHz. During the N-back task, each condition contained 15 consonants and a pause between each condition, for a total of 192 dynamic scans per run. The first 6 image volumes of the functional image dataset were discarded to allow magnetization to reach equilibrium.

Data analysis.

Statistical power.

Due to the small sample size (n = 7 per group), the power to detect statistical significance at $p < .05$ is limited to only very large effects. For example, for independent samples *t*-tests, a sample size of 7 per group would require a *t*-statistic of greater than 2.179 to reach significance at $p < .05$. This corresponds to an effect size (Cohen's *d*) of $d = 1.26$. Cohen (1988) provides guidelines for determining the magnitude of an effect size of a group comparison (Cohen's *d*), which state that effect sizes of $d = 0.2$-0.5 indicate a

small effect, effect sizes of d = 0.5-0.8 indicate a medium effect, and effect sizes of d = 0.8 or larger indicate a large effect. Therefore, in addition to discussing findings in terms of statistical significance, we will identify group differences reaching Cohen's threshold for medium and large effects.

fMRI data preparation.

All functional data were analyzed using BrainVoyager QX software (Brain Innovation B. V., Maastricht). For each participant, functional images from the participants' N-back run were corrected for 3D motion and slice-time delays, and linear trends were removed and temporally filtered. Motion correction results were assessed to ensure that all data fell within movement criteria (>3mm displacement, 3° rotation). For participants whose movement exceeded the established criterion for fewer than 1/3 of any given condition of the N-back, this data was corrected and the dynamic scans corresponding to the time points of excessive motion were removed. Individualized design matrices were generated for these participants for use in group analysis.

The functional data for each participant was aligned to the participant's high-resolution 3D anatomic dataset. Each participant's activation map was normalized to a common reference space (Talairach), using registration techniques. Following Talairach transformation, within-group GLM analyses were conducted by designing a multi-study design matrix. This analysis calculated all significantly activated voxels, both positively and negatively, during all levels of the N-back. Individual contrasts were then set, and activation at any given contrast could be examined individually. Analyses of covariance were conducted to determine whether patterns of activation differed as a whole between groups, or between different levels of the N-back, as well as to examine group by N-back

level interactions. A cluster level threshold was used to correct for multiple comparisons via 1,000 iterations of a Monte Carlo Simulation. For the current analyses, a cluster threshold of 3 functional voxels was established for examining between group interactions and main effect of group, a cluster threshold of 8 functional voxels was established for examining the main effect of N-back level, and a cluster threshold of 6 functional voxels was established for examining specific N-back level contrasts between groups. Each of these cluster thresholds maintained a significance criterion of $p < .01$. Significantly activated clusters that met this criterion were considered further. Region-of-interest (ROI) analyses were conducted using Talairach Daemon software (Lancaster et al., 2000) to determine the brain region in which significantly activated clusters occurred and the corresponding center-of-gravity coordinates in Talairach space for each relevant cluster. Composite *t*-values were calculated to measure the degree of activation in each cluster for examination of specific N-back level contrasts, and *F*-statistics were calculated to measure main effects of group and N-back level, and overall interaction effects.

Analytic plan.

Study hypotheses were analyzed as follows:

Hypothesis 1. Three independent-samples *t*-tests were conducted to examine whether brain tumor survivors performed more poorly than healthy controls on measures of executive function. Measures included the WMI, PSI, and FSIQ of the WISC-IV.

Hypothesis 2. Independent samples *t*-tests were conducted to examine whether brain tumor survivors performed more poorly than healthy controls on

the N-back task. Measures included accuracy at the 0-back, 1-back, 2-back, and 3-back conditions, as well as overall task accuracy and rates of false positives (commission errors) and omission errors. Differences in response times were also examined at individual N-back levels, and for the task overall.

Hypothesis 3. Between-group GLM and Analysis of Covariance was conducted to detect BOLD signal interactions between group and N-back level during fMRI. Significant interactions were further examined by testing specific contrast levels of the N-back task between groups. Main effect of group and main effect of N-back level were also examined.

Results

Hypothesis 1.

Means and standard deviations for measures of executive function are reported in Table 2. On the WISC-IV, mean FSIQ and WMI scores for brain tumor survivors fell within the average range, and mean PSI scores fell within the low average range. In contrast, mean WMI scores for the healthy control group fell within the average range and mean PSI and FSIQ scores fell within the high average range. Comparisons between the performance of brain tumor survivors and healthy controls, assessed using independent samples *t*-tests, indicated significant differences on the WISC-IV PSI (t = -4.07, p = .002) and WISC-IV FSIQ (t = -3.36, p = .006). Differences on the WISC-IV WMI were non-significant (t = -1.35, p = .202), although the effect size was medium (-0.72). These scores indicate that brain tumor survivors performed more poorly than healthy controls on measures of processing speed and overall cognitive ability, and effect

sizes suggest they also performed more poorly that healthy controls on measures of working memory. These findings are consistent with a recent meta-analysis (Robinson, Kuttesch, et al., 2010), documenting deficits in survivors of pediatric brain tumors of medium to large effect size.

Table 2
Group Comparisons on Measures of Executive Function During Neurocognitive Assessment[a]

	Survivors (*n = 7)*	Healthy Controls (*n = 7)*	*t*	*p*	Cohen's *d*
WISC-IV					
Working Memory	90.57 (13.94)	98.86 (8.34)	-1.35	.20	-0.72
Processing Speed	**88.57 (10.00)**	**112.43 (11.86)**	**-4.07**	**<.01**	**-2.18**
Full Scale IQ	**90.57 (8.66)**	**112.14 (14.65)**	**-3.36**	**<.01**	**-1.79**

Note. Scores on the WISC-IV are presented as standard scores (M = 100, SD = 15).
[a]Values in parentheses indicate standard deviation.

Hypothesis 2.

Means and standard deviations for measures of N-back task performance are reported in Table 3. Comparisons between the performance of brain tumor survivors and healthy controls, assessed using independent samples *t*-tests, indicated significant differences in accuracy on the 2-back (t = -2.58, p = .024) and 3-back (t = -3.33, p = .006) conditions, overall task accuracy (t = -2.56, p = .039), omission errors (t = 2.24, p = .045), and false positives (t = 2.37, p = .048) (Figure 1). Exploratory analysis of group differences in response times indicated no significant differences between groups (Figure 2). These scores indicate that, although brain tumor survivors responded within a similar time frame as healthy controls, they were more likely to make errors on the N-back task as difficulty increased, resulting in significantly poorer accuracy scores as the difficulty

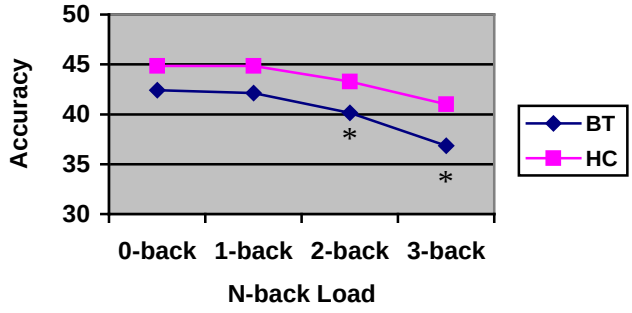
of the N-back task increased.

Table 3
Group Comparisons on N-back Performance During fMRI[a]

	Survivors (*n = 7*)	Healthy Controls (*n = 7*)	*t*	*p*	Cohen's *d*
TASK ACCURACY					
0-back Accuracy	42.43 (4.16)	44.86 (0.38)	-1.54	.15	-0.82
1-back Accuracy	42.14 (4.18)	44.86 (0.38)	-1.71	.11	-0.91
2-back Accuracy	**40.14 (2.48)**	**43.29 (2.06)**	**-2.58**	**.02**	**-1.38**
3-back Accuracy	**36.86 (2.79)**	**41.00 (1.73)**	**-3.33**	**<.01**	**-1.78**
Total Accuracy	**161.57 (12.47)**	**174.00 (3.11)**	**-2.56**	**.04**	**-1.37**
False-Positive Responses	**5.57 (3.78)**	**2.00 (1.29)**	**2.37**	**.05**	**1.27**
Omission Errors	**12.86 (9.91)**	**4.00 (3.32)**	**2.24**	**.05**	**1.20**
TASK REACTION TIME					
0-back Reaction Time	620.94 (89.39)	583.22 (96.44)	0.73	.48	0.41
1-back Reaction Time	639.38 (170.24)	567.52 (61.74)	1.05	.33	0.56
2-back Reaction Time	620.52 (91.05)	660.71 (185.53)	-0.48	.64	-0.28
3-back Reaction Time	753.36 (129.66)	835.26 (188.28)	-0.95	.36	-0.51
Total Reaction Time	655.94 (122.67)	650.73 (91.23)	0.09	.93	0.05

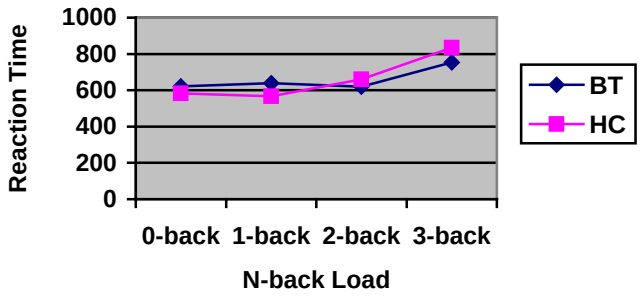
Note. Reaction times are presented in milliseconds.
[a]Values in parentheses indicate standard deviation.

Figure 1



N-back Accuracy by Load Level in Brain Tumor Survivors vs. Healthy Controls
Note. *Significant at $p < .05$

Figure 2



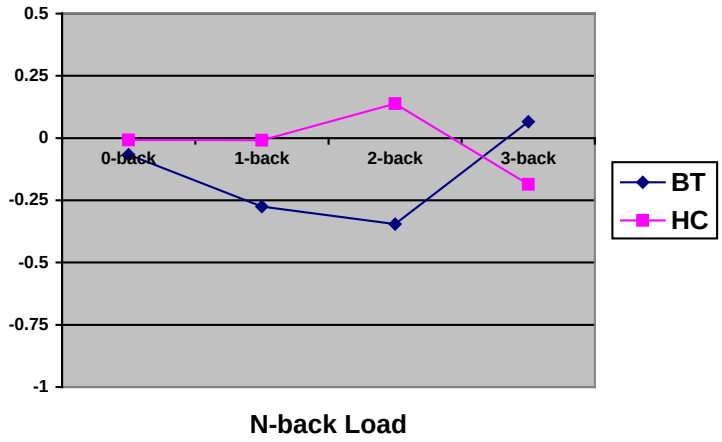
N-back Reaction Time by Load Level in Brain Tumor Survivors vs. Healthy Controls

Hypothesis 3.

A between-group GLM and analysis of covariance was conducted to determine whether brain tumor survivors and healthy controls differed in their patterns of BOLD signal activation during the N-back task. First, interactions between group and task load were examined; this yielded clusters in three brain regions where activation significantly differed by group and load level (see Table 4; Figures 3-5). These regions included the ventral ACC (BA 24), postcentral gyrus (BA 2), and supramarginal gyrus (BA 40).

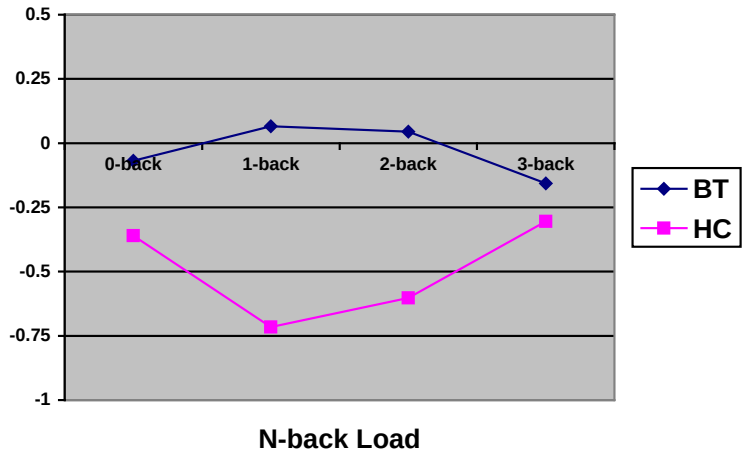
Next, between-group comparisons were conducted to examine the nature of the interaction effects. In these analyses, individual contrast levels of the N-back were entered to determine whether survivors and healthy controls differed in their recruitment of oxygenated blood to the brain regions identified in the above interaction as task difficulty increased (see Table 5). These findings indicate that, as the difficulty of the N-back increased from the 0-back to the 1-back level, patterns of activation differed between survivors and healthy controls. Specifically, survivors recruited greater amounts of oxygenated blood to the left supramarginal gyrus (BA 40), whereas healthy controls

Figure 3



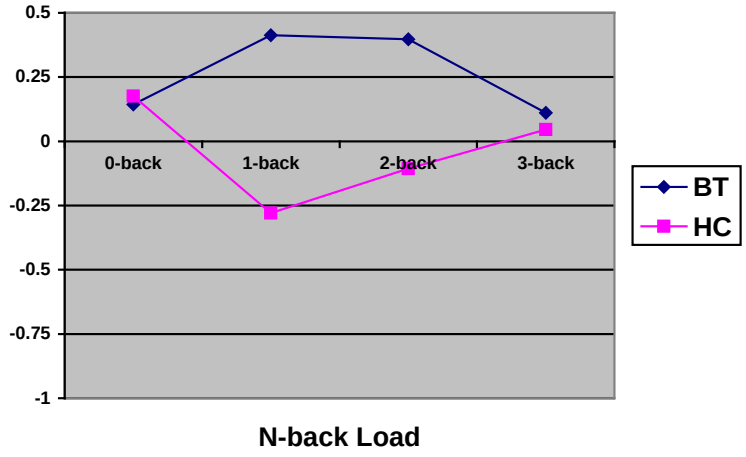
Between-Group Interaction During the N-back: Ventral Anterior Cingulate Cortex (BA 24)

Figure 4



Between-Group Interaction During the N-back: Postcentral Gyrus (BA 2)

Figure 5



Between-Group Interaction During the N-back: Supramarginal Gyrus (BA 40)

recruited lesser amounts of oxygenated blood. This region has been associated with retention of temporal information related to verbal stimuli (Owen et al., 2005). Similarly, patterns of activation differed between survivors and healthy controls in the right ventral anterior cingulate cortex (BA 24), a region that has been associated with increases in effort and attention during increasingly challenging tasks, as well as with error detection and monitoring of performance. In this region, brain tumor survivors recruited increasing amounts of oxygenated blood as task difficulty increased from the 1-back to the 3-back, and from the 2-back to the 3-back. Healthy controls, however, recruited lesser amounts of oxygenated blood to this area as difficulty increased. In contrast, whereas survivors maintained a relatively consistent level of activation in the postcentral gyrus (BA 2), healthy controls showed a significant increase in oxygenated blood as the N-back task difficulty increased from the 1-back to the 3-back level. This region is associated with processing of sensory information.

Follow-up tests of the main effect of group and the main effect of N-back load

Table 4

Significant BOLD fMRI Responses During the N-back Task: Group x Load Level Interaction

			Talairach Coordinates					
Region	Hemisphere	BA	x	y	z	*F*	*p*	# Voxels
VACC	R	24	17	-13	33	4.15	<.000001	127
PCG	L	2	-42	-18	30	3.01	<.000001	111
SMG	L	40	-52	-23	26	2.33	<.000001	118

Note. BA = Brodmann Area; VACC = Ventral Anterior Cingulate Cortex; PCG = Postcentral Gyrus; SMG = Supramarginal Gyrus; R = Right hemisphere; L = Left hemisphere.

Table 5

Significant BOLD fMRI Responses, by Contrast and Region, for Survivors and Controls During the N-back Task

				Talairach Coordinates					
	Region	Hemisphere	BA	x	y	z	*t*	*p*	# Voxels
Survivors > Controls									
1-back v 0-back	SMG	L	40	-52	-25	25	6.01	<.001	424
3-back v 1-back	VACC	R	24	19	-13	34	3.56	.004	178
3-back v 2-back	VACC	R	24	17	-13	33	4.63	.001	458
Controls > Survivors									
3-back v 1-back	PCG	L	2	-45	-18	28	-4.42	.001	794

Note. BA = Brodmann Area; SMG = Supramarginal Gyrus; VACC = Ventral Anterior Cingulate Cortex; PCG = Postcentral Gyrus; R = Right hemisphere; L = Left hemisphere.

were also conducted. No significant between-group differences were found for the overall main effect of group. In analyses of the whole sample, 16 clusters were identified where BOLD signal activation differed as a function of N-back load, regardless of participant group. These clusters indicate that during the N-back task, as a whole, participants recruited increased oxygenated blood bilaterally to the medial frontal gyrus (BA 6), superior parietal lobule (BA 7), and supramarginal gyrus (BA 40), as well as to the right superior frontal gyrus (BA 8) and dorsal anterior cingulate cortex (BA 32). In analyses of the whole sample, participants also recruited increased oxygenated blood to the left dorsolateral prefrontal cortex (BA 9), parahippocampal gyrus (BA 30), dorsal posterior cingulate cortex (BA 31), and secondary visual cortex (BA 18). Activation in these areas is largely consistent with patterns of responding often seen during verbal N-back tasks (Owen et al., 2005) and suggests that, as a whole, participants were actively engaged in this task during fMRI.

Discussion: Study I

The above results indicate that we were able to successfully identify a sample of survivors of pediatric brain tumors who showed deficits in performance on cognitive tests compared with a matched sample of healthy controls in a pattern that is consistent with a recent meta-analysis (Robinson, Kuttesch, et al., 2010). The deficits documented in this sample are consistent in both direction and magnitude with the literature on late-effects in survivors.

Because of deficits in processing speed and overall cognitive ability, it was expected that survivors would have difficulty, relative to healthy children, on the N-back

task. In our sample, survivors performed similarly to healthy children during the easiest levels of the N-back, but as task difficulty increased, they were unable to maintain this level of performance. This indicates that we were able to select a task that was sensitive to the types of deficits experienced by brain tumor survivors.

The examination fMRI data related to the main effect of N-back load level across group, indicated that as a whole, participants showed brain activation in regions commonly associated with this verbal working memory task (Owen et al., 2005). The engagement of these regions during the N-back task, in the absence of a main effect of group, provides further evidence that although differences in performance were noted, both survivors and healthy controls were actively engaged in this task. This suggests that differences in the magnitude of activation at individual contrast levels is indicative of differences in cognitive effort to complete the N-back, rather than an overall lack of attending to the task in one group relative to another. Finally, differences in activation in this sample of childhood brain tumor survivors indicates that survivors may require increased resources (i.e., oxygenated blood) relative to healthy children to brain regions associated with complex working memory processes.

These findings suggest that neurobiological differences distinguish brain tumor survivors from healthy children, and raises questions regarding the association between these neurobiological underpinnings and deficits in psychosocial functioning. In particular, survivors may struggle with skills that rely on executive function for successful completion. These associations are examined in Study II.

CHAPTER III

Study II

The goals of Study II were to examine variability in executive and psychosocial functioning within a larger sample of survivors of pediatric brain tumors, and to examine the associations between indicators of survivors' psychosocial functioning and BOLD signal activation during a verbal working memory task administered during fMRI. First, preliminary analyses were conducted to examine the association between coping and psychosocial functioning in brain tumor survivors. Next, the following specific hypotheses were tested:

Hypothesis 1. Consistent with literature on late effects of pediatric brain tumor, survivors will exhibit poor performance, relative to normative data, on measures of neurocognitive and executive function, including the areas of working memory, processing speed, overall cognitive ability. Survivors will also show deficits, relative to normative data, on measures of psychosocial and emotional functioning.

Hypothesis 2. In response to a working memory task, brain tumor survivors will show an increase in oxygenated blood to *a priori* selected regions of interest as task difficulty increases. Regions of interest for these analyses will be identified via three mechanisms. First, regions identified in Study I as more activated, relative to healthy controls, will be considered. These include the ventral anterior cingulate cortex (BA 24) and supramarginal gyrus (BA 40).

Second, a previous study examined activation during a verbal N-back task in survivors of ALL (Robinson, Livesay, et al., 2010), a population in which similar patterns of late-effects have been identified (Campbell et al., 2007). In this study, the dorsolateral prefrontal cortex (BA 9) and dorsal anterior cingulate cortex (BA 32) were identified as regions associated with patterns of compensatory activation, and will therefore be examined here. Finally, additional regions identified in a meta-analysis of studies using a verbal N-back task will be examined (Owen et al., 2005). These include the lateral premotor cortex (BA 6), ventrolateral prefrontal cortex (BA 44), anterior prefrontal cortex (BA 10), superior parietal lobule (BA 7), and superior frontal gyrus (BA 8).

Hypothesis 3. BOLD signal activation during fMRI will be associated with the ways that brain tumor survivors cope with stress, as well as survivors' psychosocial and emotional functioning. Specifically, increased recruitment of oxygenated blood to *a priori* regions of interest identified above (see Hypothesis 2) will be associated with use of engagement forms of coping (i.e., primary and secondary control coping) and less use of disengagement coping. Increases in activation will also be associated with higher social competence and lower rates of social problems and internalizing symptoms (e.g., anxiety, depression).

Method

Participants.

Twenty-one children who had been treated for a childhood brain tumor and who were at least 2 years post-diagnosis participated in a study of the neurocognitive

functioning of survivors of pediatric brain tumor. For the present analyses, 17 survivors (6 girls) for whom complete data was available were included. Three survivors' data was excluded due to missing N-back task performance data during the fMRI session resulting from a computer error, and one survivor's data was excluded due to the participant's excessive motion during the fMRI scan. Survivors were identified through the Childhood Cancer Survivorship Clinic in the Department of Pediatric Hematology/Oncology, or the Department of Neurology, at Vanderbilt University Monroe Carrel Jr. Children's Hospital.

Sixteen survivors were Caucasian, and one was African American. Upon enrollment in the study, survivors were on average 12.59 years old (SD = 2.48). Survivors were diagnosed at 6.94 years old (SD = 2.41; range 2.06-11.62 years) with a brain tumor, and were on average 5.64 years post-diagnosis (SD = 2.90; range 2.14-10.92 years). Tumor pathologies included juvenile pilocytic astrocytoma (*n* = 9), posterior fossa medulloblastoma (*n* = 4), dysembryoplastic neuroepithelial tumor (*n* = 3), and craniopharyngioma (*n* = 1). All procedures were approved by the Institutional Review Board, and informed consent and assent were obtained from all participants.

Procedure.

For details on study enrollment and procedures, see Study I.

Measures.

Neurocognitive assessment.

For these analyses, in addition to participants' scores on the WMI, PSI, and FSIQ of the WISC-IV (see Study I for description), several additional questionnaire measures will be examined. At their assessment session, children and parents returned completed

questionnaire packets prior to beginning the neurocognitive assessment. Parents completed several questionnaires providing information about the family overall, as well as the survivor in particular. Survivors also completed measures about their own functioning.

Emotional and behavioral problems.

Parents provided information about brain tumor survivors' social, emotional and behavioral problems by completing the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), a measure of symptoms of anxiety/depression, social problems, and disruptive behavior problems in children and adolescents. Children completed the Youth Self-Report (YSR; Achenbach & Rescorla, 2001), the self-report version of the CBCL to further assess for symptoms of emotional and behavioral problems. These scales have strong test-retest reliability and criterion validity. In the following analyses, social problems and internalizing symptoms will be assessed using the Social Competence, Anxious/Depressed, and Social Problems scales.

Coping.

Parents and children also completed the Social Stress version of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000) as a measure of coping and stress reactivity associated with stress related to interpersonal and peer relationships. This questionnaire asks parents and children to report the frequency with which children were exposed to a variety of stressors associated with social relationships and the ways in which the children cope with these stressors. Based on previous research on the association between coping and executive function (Campbell et al., 2009), the current study focuses on coping responses comprising the three coping domains: Primary Control

coping (i.e., problem solving, emotional modulation, emotional expression), Secondary Control coping (i.e., acceptance, cognitive restructuring, positive thinking, distraction), and Disengagement coping (i.e., avoidance, denial, wishful thinking). The RSQ has been shown to have good test-retest reliability (alphas ranged from .69 to .81) and internal consistency (alphas ranged from .67 to .92); convergent and discriminant validity have been established (e.g., Connor-Smith et al., 2000).

Functional neuroimaging.

For details on the N-back task, see Study I. For these analyses, within-group BOLD signal activation during the N-back task will be examined.

Image acquisition.

For details on image acquisition, see Study I.

Data analysis.

Statistical power.

Due to the sample size (n = 17), the power to detect statistical significance at $p <$ .05 is limited to only potentially medium to large effects. For example, for correlation analyses, a sample size of 17 requires a correlation of greater than 0.483 to reach significance at $p < .05$. Cohen (1992) provides guidelines for determining the effect size of a Pearson correlation, which state that correlations of $r = 0.1$ to 0.23 indicate a small effect, correlations of $r = 0.24$ to 0.36 indicate a medium effect, and correlations of $r =$ 0.37 or larger indicate a large effect. With a sample of 17 survivors, a correlation of .37 corresponds to $p = 0.14$ for large effects. For each set of analyses, in addition to discussing findings in terms of statistical significance, we will identify correlations reaching Cohen's threshold for large effects.

Additionally, in order to ensure that outliers on a given measure were not disproportionately influencing the magnitude of correlations, each measure was reviewed to detect the presence of outliers in the data. Significant outliers included data points where a participant's score fell greater than 2 standard deviations away from the group mean for a given measure or subscale. When outliers were identified, the data set was adjusted such that the participant's scores would not be included in analyses dependent on the measure in question. After these steps were taken, sample sizes for correlations ranged from 15-17. This means that, when sample size was most limited (i.e., $n = 15$), a correlation of greater than 0.514 was required to reach statistical significance at $p < .05$. Large effects of $r = 0.37$ or greater, based on Cohen's (1992) guidelines, correspond to $p < 0.18$.

fMRI data preparation.

For information on preprocessing, motion correction, and normalization of raw imaging data, see Study I. Following Talairach transformation, within-group GLM analyses were conducted by designing a multi-study design matrix. This analysis calculated all significantly activated voxels, both positively and negatively, during all levels of the N-back. Individual contrasts were then set, and activation at any given contrast could be examined individually. A cluster level threshold was used to correct for multiple comparisons via 1,000 iterations of a Monte Carlo Simulation. For the current analyses, a cluster threshold of 3 functional voxels was established for examining within-group patterns of BOLD signal activation. This cluster threshold maintained a significance criterion of $p < .001$. Significantly activated clusters that met this criterion were considered further. Region-of-interest analysis was conducted using Talairach

Daemon software (Lancaster et al., 2000) to determine the brain region in which significantly activated clusters occurred and the corresponding center-of-gravity coordinates in Talairach space for each relevant cluster. Composite *F*-statistics were calculated to measure the degree of activation in each cluster and overall region.

Analytic plan.

Study II: Preliminary analyses.

Preliminary analyses were conducted to examine the association between coping and psychosocial functioning in pediatric brain tumor survivors.

Study II: Main analyses.

Study hypotheses were analyzed as follows:

Hypothesis 1. A series of one-sample *t*-tests were conducted to examine whether brain tumor survivors performed more poorly than published normative data on measures of executive and psychosocial functioning. Measures included the WMI, PSI, and FSIQ of the WISC-IV, and the Social Competence, Anxious/Depressed, and Social Problems scales of the CBCL and YSR.

Hypothesis 2. Within-group GLM was conducted to examine changes in BOLD signal activation at increasingly difficult levels of the N-back. N-back level contrasts were made by comparing activation on more difficult levels of the N-back, relative to activation on less difficult levels. Specifically, changes in BOLD signal in the ventral anterior cingulate cortex (BA 24), supramarginal gyrus (BA 40), dorsolateral prefrontal cortex (BA 9), dorsal anterior cingulate cortex (BA 32), lateral premotor cortex (BA 6), ventrolateral prefrontal cortex (BA 44), anterior prefrontal cortex (BA 10), superior parietal lobule (BA 7), and

superior frontal gyrus (BA 8) were examined.

Hypothesis 3. Pearson correlations were conducted to assess the association between BOLD signal activation in significantly activated clusters identified in Hypothesis 2 and measures of psychosocial functioning, including coping and social and emotional problems.

Results

Preliminary analyses.

As expected, the use of engagement coping (i.e., primary and secondary control coping) was found to be associated with higher social competence, and lower rates of social problems and internalizing symptoms (e.g., anxiety, depression). The use of disengagement coping was found to be associated with lower social competence, and higher rates of social problems and internalizing symptoms (see Table 6).

Table 6
Correlations Among Coping and Psychosocial Functioning on the CBCL and YSR

	Parent – Primary	Parent – Secondary	Parent – Disengagement	Self – Primary	Self – Secondary	Self - Disengagement
CBCL SocComp	.14	**.55***	-.28	.16	.18	-.36
CBCL AnxDep	-.09	-.30	.34	-.07	-.13	.36
CBCL SocProb	-.11	-.27	.18	-.20	-.11	.06
YSR SocComp	-.19	**.49+**	.06	.08	.08	**-.38+**
YSR AnxDep	-.11	**-.52***	**.46+**	**-.60***	**-.75****	**.60***
YSR SocProb	-.03	**-.40+**	.34	**-.57***	**-.89****	**.57***

Note. CBCL = Child Behavior Checklist; YSR = Youth Self Report; SocComp = Social Competence Scale; AnxDep = Anxious/Depressed Scale; SocProb = Social Problems Scale.
**Significant at $p < .01$; *Significant at $p < .05$; +Non-significant Large Effect.

Specifically, survivors' self-report of their use of primary control coping strategies was significantly negatively associated with their self-report on the anxious/depressed (r = -.60, p = .011) and social problems (r = -.57, p = .016) scales on the YSR. Similarly,

survivors' self-report of their use of secondary control coping strategies was significantly negatively associated with their self-report on the anxious/depressed (r = -.75, p = .001) and social problems (r = -.89, p < .001) YSR scales. Parents' report of their children's use of secondary control coping strategies was significantly associated with their report of children's social competence (r = .55, p = .021), and children's self-report on the anxious/depressed scale (r = -.52, p = .032). Large but non-significant effects were also found for the association between parents' report of their children's use of secondary control coping and children's self-report of social competence (r = .49, p = .052), as well as children's self-report on the social problems scale (r = -.40, p = .111).

When survivors reported on their own use of disengagement coping, significant negative correlations were found between coping and survivors' self-report on the anxious/depressed (r = .60, p = .010) and social problems (r = .57, p = .017) scales. A large, but non-significant, negative effect was found for survivors' self-report of their use of disengagement coping strategies and their self-report of social competence (r = -.38, p = .143). Finally, when parents reported of children's use of disengagement coping strategies, a large effect was found for the association between coping and children's self-report on the anxious/depressed scale (r = .46, p = .064). Overall, these associations between psychosocial functioning and coping suggest that, among this sample of survivors of pediatric brain tumors, use of primary and secondary control coping is associated with greater social competence and fewer symptoms of anxiety, depression, and social difficulties, whereas use of disengagement coping is associated with poorer social competence and increased symptoms of anxiety, depression, and social difficulties.

Hypothesis 1.

Means and standard deviations for measures of executive function are reported in Table 7.

Table 7
Means, Standard Deviations, and One-Sample t-tests of Measures of Executive and Psychosocial Functioning, and Coping[a]

	Survivors (n = 17)	t	p	Cohen's d
Neurocognitive Assessment				
WISC-IV				
Working Memory	**90.94 (12.47)**	**-3.00**	**.009**	**-0.66**
Processing Speed	**84.12 (9.82)**	**-6.67**	**<.001**	**-1.25**
Full Scale IQ	**91.82 (13.05)**	**-2.58**	**.020**	**-0.58**
Parent Report				
CBCL				
Social Competence	**41.53 (8.00)**	**-4.37**	**<.001**	**-0.95**
Anxious/Depressed	**59.94 (8.22)**	**4.99**	**<.001**	**1.09**
Social Problems	**62.71 (6.96)**	**7.53**	**<.001**	**1.48**
RSQ				
Primary Control	.21 (.03)			
Secondary Control	.24 (.05)			
Disengagement	.16 (.03)			
Child Self-Report				
YSR				
Social Competence	**42.00 (8.36)**	**-3.83**	**.002**	**-0.87**
Anxious/Depressed	**58.47 (10.60)**	**3.29**	**.005**	**0.82**
Social Problems	**60.18 (7.87)**	**5.33**	**<.001**	**1.13**
RSQ				
Primary Control	.18 (.04)			
Secondary Control	.26 (.06)			
Disengagement	.16 (.02)			

Note. CBCL = Child Behavior Checklist; YSR = Youth Self Report; RSQ = Responses to Stress Questionnaire; Scores on the WISC-IV are presented as standard scores (M = 100, SD = 15). Scores on the CBCL and YSR are presented as T scores (M = 50, SD = 10). One-sample *t*-tests compared brain tumor survivors' WISC-IV scores with a population mean of 100, and CBCL and YSR scores with a population mean of 50. Scores on the RSQ are presented as ratio scores.
[a]Values in parentheses indicate standard deviation.

On the WISC-IV, mean FSIQ and WMI scores for survivors of pediatric brain tumors fell

within the average range, and PSI mean scores fell within the low average range. When WISC-IV scores were compared with published normative data using one-sample *t*-tests, results indicated that survivors' mean WMI (t = -3.00, p = .009), PSI (t = -6.67, p < .001), and FSIQ (t = -2.58, p = .020) scores were significantly below norms, indicating more problems in all of these areas of functioning. This is consistent with the pattern of deficits documented in survivors of pediatric brain tumors (Robinson, Kuttesch, et al., 2010).

Means and standard deviations for measures of psychosocial functioning and coping are also reported in Table 7. When mean CBCL and YRS scores were compared with published normative data using one-sample *t*-tests, results indicated that survivors' mean scores fell significantly above the norm on all problem scales, and significantly below the norm on competency scales, based on both parent report and child self-report (see Table 7). This suggests that brain tumor survivors experience more symptoms of anxiety/depression and social problems, and are less competent socially, than is expected based on normative data.

Hypothesis 2.

Within-group GLM analyses were conducted to examine changes in BOLD signal activation at increasingly difficult levels of the N-back task. Levels of activation for the contrasting load demands for the N-back tasks are presented separately for the sample of survivors in Table 8, as well as in Figures 6 and 7. When regions identified in Study I as more activated relative to healthy controls were examined, results indicated that brain tumor survivors recruited significantly greater amounts of oxygenated blood to the right supramarginal gyrus (BA 40) as N-back difficulty increased from the 0-back to the 3-

Table 8

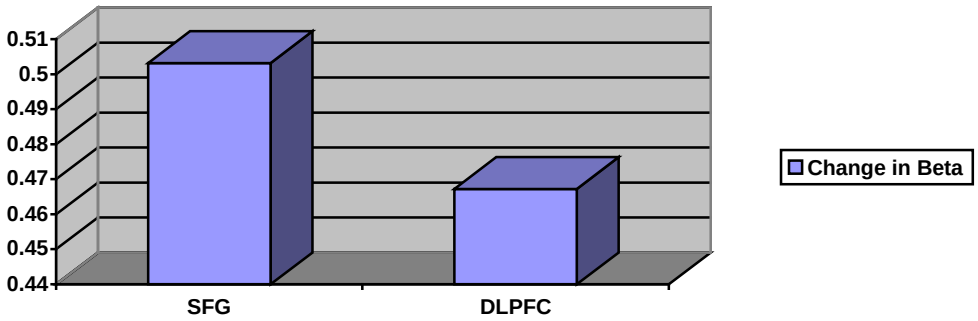
Significant Within-Group BOLD fMRI Responses During the N-back Task

				Talairach Coordinates					
	Region	Hemisphere	BA	x	y	z	*t*	*p*	# Voxels
2-back v 0-back	SFG	R	8	1.6	17	47	6.35	<.001	96
	DLPFC	L	9	-39	7.4	30	6.32	<.001	92
3-back v 0-back	APFC	R	10	37	44	21	7.80	<.001	157
	SMG	R	40	32	-53	36	5.93	<.001	339
	DACC	R	32	8.8	21	39	7.19	<.001	117

Note. BA = Brodmann Area; SFG = Superior Frontal Gyrus; SVC = Secondary Visual Cortex; DLPFC = Dorsolateral Prefrontal Cortex; APFC = Anterior Prefrontal Cortex; SMG = Supramarginal Gyrus; DACC = Dorsal Anterior Cingulate Cortex; R = Right hemisphere; L = Left hemisphere.

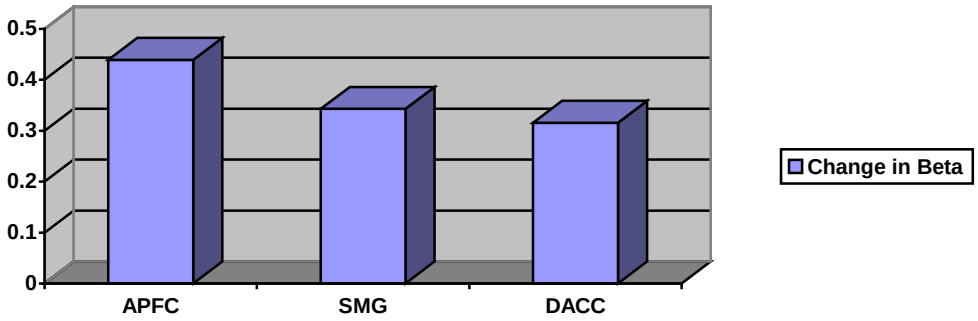
back condition ($p < .001$). No significant within-group differences in activation were found for the ventral anterior cingulate cortex (BA 24).

Figure 6



Within-Group Changes in Activation During the N-back: 0-back vs. 2-back

Figure 7



Within-Group Changes in Activation During the N-back: 0-back vs. 3-back

Next, regions identified in a study of brain activation during a verbal N-back in survivors of leukemia (Robinson, Livesay, et al., 2010) were examined. Within this sample of brain tumor survivors, significantly greater amounts of oxygenated blood were recruited to the left dorsolateral prefrontal cortex (BA 9) as task difficulty increased from

the 0-back to the 2-back, and greater amounts of oxygenated blood were recruited to the right dorsal anterior cingulate cortex (BA 32) as task difficulty increased from the 0-back to the 3-back (all $p < .001$).

Finally, when regions identified in a recent meta-analysis of studies using a verbal N-back task were examined (Owen et al., 2005), results indicated that brain tumor survivors recruited significantly greater amounts of oxygenated blood to the right superior frontal gyrus (BA 8) as task difficulty increased from the 0-back to the 2-back condition, and to the right anterior prefrontal cortex (BA 10) as task difficulty increased from the 0-back to the 3-back condition (all $p < .001$). No significant within-group differences in activation were found for the premotor cortex (BA 6), ventrolateral prefrontal cortex (BA 44), or superior parietal lobule (BA 7).

Each of these significantly activated regions has been consistently documented to activate during completion of the N-back task (Owen et al., 2005) and underlie functions including higher-level organization of information (BA 9), simultaneous processing of multiple cognitive tasks (BA 10), retaining temporal information regarding visual and verbal stimuli (BA 40), maintenance of visuospatial attention (BA 8), and complex problem solving (BA 32). The association between activation in these five regions and survivors' psychosocial functioning is explored below.

Hypothesis 3.

Bivariate Pearson correlations between BOLD signal activation and coping can be found in Table 9. When use of secondary control coping was examined, significant, positive correlations were found between parents' report of survivors' use of secondary control coping and activation in the anterior prefrontal cortex (BA 10; $r = .67$, $p = .003$),

and between survivors' self-reported use of secondary control coping and activation in the superior frontal gyrus (BA 8; $r = .60$, $p = .014$). Additionally, large but non-significant effects were found for the association between parents' report of survivors' use of secondary control coping and activation in the dorsal anterior cingulate cortex (BA 32; $r = .36$, $p = .168$), as well as between survivors' self-reported use of secondary control coping and activation in the dorsolateral prefrontal cortex (BA 9; $r = .48$, $p = .053$) and dorsal anterior cingulate cortex (BA 32; $r = .42$, $p = .106$).

Table 9
Correlations Among BOLD Signal Activation and Coping

	SFG – R	DLPFC – L	APFC – R	SMG – R	DACC – R
Parent-Primary Control	.09	.14	.08	-.09	.26
Parent-Secondary Control	.20	.05	**.67****	.36	**.36+**
Parent-Disengagement	-.33	**-.52***	-.32	-.00	-.27
Self-Primary Control	.24	.36	**.37+**	-.19	**.39+**
Self-Secondary Control	**.60***	**.48+**	.30	-.31	**.42+**
Self-Disengagement	**-.68****	**-.47+**	-.31	.06	**-.57***

Note. SFG – R = Superior Frontal Gyrus (BA 8), right hemisphere; DLPFC – L = Dorsolateral Prefrontal Cortex (BA 9), left hemisphere; APFC – R = Anterior Prefrontal Cortex (BA 10), right hemisphere; SMG – R = Supramarginal Gyrus (BA 40), right hemisphere; DACC – R = Dorsal Anterior Cingulate Cortex (BA 32), right hemisphere.
**Significant at $p < .01$; *Significant at $p < .05$; +Non-significant Large Effect.

When use of primary control coping was examined, no significant effects were found. However, large but non-significant effects were found for the association between survivors' self-reported use of these coping strategies and recruitment of oxygenated blood to the anterior prefrontal cortex (BA 10; $r = .37$, $p = .143$) and dorsal anterior cingulate cortex (BA 32; $r = .39$, $p = .139$). These findings suggest that selection of more adaptive, but cognitively complex, coping strategies is associated with increased recruitment of oxygenated blood to brain regions underlying similar skills during a verbal

working memory task.

Parents' report of survivors' use of disengagement coping was found to be significantly negatively associated with recruitment of oxygenated blood to the dorsolateral prefrontal cortex (BA 9; r = -.52, p = .032). Further, survivors' self-reported use of disengagement coping was significantly negatively associated with recruitment of oxygenated blood to the superior frontal gyrus (BA 8; r = -.68, p = .004) and dorsal anterior cingulate cortex (BA 32; r = -.57, p = .021). A large but non-significant effect was found for survivors' self-reported use of disengagement coping and activation in the dorsolateral prefrontal cortex (BA 9; r = -.47, p = .058). Each of these correlations indicates that, as activation increases in a given brain region brought on-line during completion of a verbal working memory task, survivors' use of primary control coping and/or secondary control coping also increases, whereas survivors' use of disengagement coping decreases.

Bivariate Pearson correlations were also conducted to assess the relationship between BOLD signal activation in *a priori* regions of interest and psychosocial functioning (see Table 10). With regard to survivors' social competence, results indicated that parents' reports of survivors' social competence were significantly positively associated with increases in activation in the anterior prefrontal cortex (BA 10; r = .57, p = .018). This indicates that survivors rated by parents as being more competent in the social domain recruited greater amounts of oxygenated blood to this region as the difficulty of the N-back task increased.

Parents' reports of survivors' internalizing symptoms on the anxious/depressed scale were found to be significantly negatively associated with increases in activation in

the superior frontal gyrus (BA 8; r = -.55, p = .032) and the dorsolateral prefrontal cortex (BA 9; r = -.62, p = .010). Survivors' self-reports of internalizing on the anxious/depressed scale were found to be significantly negatively associated with increases in activation in the anterior prefrontal cortex (BA 10; r = -.59, p = .012). Additionally, large but non-significant negative effects were found for the association between survivors' self-reports of internalizing on the anxious/depressed scale and increases in activation in the superior frontal gyrus (BA 8; r = -.42, p = .105), dorsolateral prefrontal cortex (BA 9; r = -.47, p = .058), and dorsal anterior cingulate cortex (BA 32; r = -.47, p = .066).

Table 10
Correlations Among BOLD Signal Activation and Psychosocial Functioning on the CBCL and YSR

	SFG – R	DLPFC – L	APFC – R	SMG – R	DACC – R
CBCL SocComp	.29	-.24	**.57***	.16	.33
CBCL AnxDep	**-.55***	**-.62****	-.01	-.24	-.18
CBCL SocProb	-.29	-.14	.11	-.26	.11
YSR SocComp	.30	-.21	.25	.26	.33
YSR AnxDep	**-.42+**	**-.47+**	**-.59***	-.09	**-.47+**
YSR SocProb	**-.46+**	**-.37+**	**-.44+**	.25	**-.42+**

Note. SFG – R = Superior Frontal Gyrus (BA 8), right hemisphere; DLPFC – L = Dorsolateral Prefrontal Cortex (BA 9), left hemisphere; APFC – R = Anterior Prefrontal Cortex (BA 10), right hemisphere; SMG – R = Supramarginal Gyrus (BA 40), right hemisphere; DACC – R = Dorsal Anterior Cingulate Cortex (BA 32), right hemisphere; CBCL = Child Behavior Checklist; YSR = Youth Self Report; SocComp = Social Competence Scale; AnxDep = Anxious/Depressed Scale; SocProb = Social Problems Scale.
**Significant at p < .01; *Significant at p < .05; +Non-significant Large Effect

When parents' and survivors' ratings on a scale assessing social problems were examined, large but non-significant negative effects were found for the association between survivors' self-ratings on the social problems scale and increases in activation in the superior frontal gyrus (BA 8; r = -.46, p = .070), dorsolateral prefrontal cortex (BA 9; r = -.37, p = .150), anterior prefrontal cortex (BA 10; r = -.44, p = .080) and dorsal

anterior cingulate cortex (BA 32; r = -.42, p = .109). These associations indicate that survivors who recruited greater amounts of oxygenated blood to the regions-of-interest identified in this study were less likely to experience symptoms of anxiety and depression, and struggle in the area of social functioning.

CHAPTER IV

Discussion

The treatment of brain and CNS malignancies and other childhood cancers reflects a double-edged sword (Rosoff, 2006). On the one hand, significant advances in treatment have led to dramatically improved rates of survival. On the other hand, however, these aggressive methods of treatment are associated with significant long-term adverse effects, including deficits in neurocognitive and socioemotional functioning. The current studies are among the first to use functional neuroimaging methods to better understand the nature and extent of these effects in childhood survivors of brain and CNS tumors. The findings suggest that survivors suffer impairment in function in prefrontal and inferior parietal regions of the brain, and that these impairments are linked to deficits emotional, social cognitive, and interpersonal functioning.

The current studies began by examining the differences in neurocognitive functioning in a sample of survivors of pediatric brain tumors relative to healthy children. Additionally, survivors and healthy children completed a verbal working memory task while undergoing fMRI, allowing for the comparison of both task performance and brain activation during engagement in a measure of executive function. It was expected that survivors would perform more poorly than healthy children on measures of neurocognitive functioning and on the verbal working memory task administered in the scanner. Based on previous studies documenting compensatory activation in childhood cancer survivors and other chronically ill populations with neurocognitive deficits (e.g.,

Robinson, Livesay, et al., 2010; Sweet, Rao, Primeau, Durgerian, & Cohen, 2006), it was expected that survivors would recruit greater amounts of oxygenated blood than healthy controls to areas of the brain associated with working memory task completion.

Despite a small sample size for between-group analyses, we found that survivors of pediatric brain tumors performed significantly more poorly than healthy controls on measures of processing speed and overall cognitive ability. Although not statistically significant, survivors also performed on average over 8 points lower than healthy controls on a measure of working memory, with a corresponding effect size of -0.72. This suggests that survivors are experiencing deficits in overall cognitive ability, as well as executive function, which are consistent with literature documenting patterns of neurocognitive late effects in survivors (Robinson, Kuttesch, et al., 2010).

Examination of the individual scores on measures of cognitive ability indicates that there was quite a range of functioning within this sample of survivors. For example, on the WMI, survivors' scores ranged from 71, which falls in the borderline range and corresponds to the 3rd percentile of a normative sample, to 110, which falls in the average range and corresponds to the 75th percentile. This highlights the need for examination of the range of deficits experienced by survivors of pediatric brain tumors, as well as mediators and moderators of risk. By identifying the subset of survivors most at risk for developing neurocognitive late effects, future interventions can be developed that target those survivors most in need.

On the N-back task, a well-established measure of working memory, survivors performed significantly more poorly than healthy children as the task became more difficult. Specifically, survivors made significantly more errors, and had correspondingly

worse scores on measures of accuracy at the 2-back and 3-back levels. In contrast, there was no difference in performance on the 0-back and 1-back levels of the N-back. This indicates that survivors were able to complete the task accurately when the cognitive demand was low. However, as the complexity of the task increased, they were unable to maintain the same level of performance, whereas the healthy children were able to consistently complete the task with a high degree of accuracy. A similar pattern was observed in survivors of acute lymphocytic leukemia (Robinson, Livesay, et al., 2010), a population in which similar patterns of neurocognitive late effects have been documented. In this study, survivors of leukemia performed similarly to healthy controls on the 0-back and 1-back conditions and a trend was observed for poorer performance on the 2-back and 3-back levels.

Brain tumor survivors made significantly more errors of omission and false-positive responses than healthy controls, indicating that they were more likely to both respond to an item that was not indicated and fail to respond when a response was indicated. Importantly, this pattern of responding suggests that survivors continued to be actively engaged in the task. In other words, their diminished accuracy was not simply due to an absence of any responding at all during difficult levels of the N-back, but rather they were less able to distinguish whether a given stimulus required a response.

Between-group analyses of BOLD signal activation during the N-back task indicated that survivors recruited greater amounts of oxygenated blood to the left supramarginal gyrus (BA 40) as N-back difficulty increased from the 0-back to the 1-back level, and to the right ventral anterior cingulate cortex (BA 24) as N-back difficulty increased from the 1-back and the 2-back levels to the 3-back level. These differences in

activation indicate that survivors required significantly more oxygenated blood recruited to areas associated with N-back completion (Owen et al., 2005) in order to complete the task. Although neurocognitive deficits have been well established in survivors of pediatric brain tumors, this is the first known study to examine these processes at a neurobiological level.

The supramarginal gyrus (BA 40) is located in the inferior parietal lobe, and this region has been reported to activate concomitantly with areas of the prefrontal cortex during working memory tasks (e.g., Awh et al., 1996; Owen, Evans, & Petrides, 1996). It has been posited that this region is active during these activities due to its role in the storage and rehearsal mechanisms central to completion of working memory tasks. Specifically, it is thought that this area is involved in a circuit of regions mediating shifts of attention necessary for mental rehearsal of verbal information (Jonides et al., 1998). The fact that brain tumor survivors evidenced increased recruitment to this region on the 1-back, a level fairly low in difficulty, indicates they may need to rely on mental rehearsal strategies earlier than healthy controls, who showed a drop in activation in this area from the 0-back to the 1-back, and subsequent increases as task difficulty rose.

The anterior cingulate cortex (BA 24) has been found to activate in response to tasks that require increasing amounts of effort, attention, or are increasing in complexity (Duncan & Owen, 2000). Further, studies have associated this region with maintaining attention despite competing task demands, and monitoring of one's performance, including error detection and monitoring (Rama et al., 2001). The pattern of activation in this region in the current study indicates that, whereas healthy controls maintained a fairly consistent pattern of activation at the 0-back, 1-back, and 2-back levels, and

showed a decrease in activation at the 3-back level, survivors of pediatric brain tumors recruited lower levels of oxygenated blood to this region at simpler levels of the N-back, but activation sharply increased when task difficulty increased from the 2-back to the 3-back. The fact that survivors recruited oxygenated blood to the anterior cingulate cortex only on this most difficult level may be indicative of compensatory activation, in which survivors required an increase in resources to this region in order to manage the increase in cognitive load. Alternatively, this region has been found to activate during performance monitoring and error detection (e.g., Kiehl, Liddle, & Hopfinger, 2000; Menon, Adleman, White, Glover, & Reiss, 2001; Rama et al., 2001), and this activation may indicate that survivors were aware of their poorer performance on the more difficult levels of the task. Examination of the association between activation in this region and accuracy on the N-back may be helpful in further understanding the functional processes underlying this pattern of activation.

Patterns of activation in the postcentral gyrus (BA 2) differed significantly between survivors and healthy controls. Specifically, whereas brain tumor survivors maintained a relatively consistent level of activation in this region, healthy controls evidenced an initial decrease in activation from the 0-back to the 1-back, and subsequent increases in activation such that their level of activation on the 3-back was roughly equal to the level of activation on the 0-back (i.e., they returned to baseline). The postcentral gyrus has been associated with the detailed processing of proprioceptive and tactile information (Dykes, 1978; Pause, Kunesch, Binkofski, & Freund, 1989). Studies of brain regions underlying successful working memory task completion have not implicated this region, and therefore its role in healthy controls' completion of this task is unclear.

Further research should monitor activation in this region to determine whether this effect was the product of a small sample size or whether this region subserves a particular function within samples of typically developing children and adolescents.

These initial between-group analyses confirmed that survivors of pediatric brain tumors and healthy children differ in their neurocognitive function in response to a working memory task, and our analyses of BOLD signal activation in this group revealed that survivors and healthy controls differ at a neurobiological level as well. Interestingly, quite a bit of variability was observed within this small sample of survivors, suggesting that additional analyses with a larger sample are warranted.

The second study provided further examination of the range of deficits experienced by brain tumor survivors. Because it has been well established that brain tumor survivors experience deficits in a range of areas including psychosocial and emotional functioning, the association between the unique neurobiological processes of this sample of brain tumor survivors (i.e., BOLD signal activation during fMRI) and these areas of functioning was explored. The first step in examining the associations between neurocognitive, psychosocial and emotional functioning, and coping in survivors of pediatric brain tumors was to examine the relationship between psychosocial/emotional functioning and the ways that childhood brain tumor survivors cope with stress in peer relationships. In other populations, use of primary and secondary control coping responses have been found to be associated with better psychological adjustment, whereas disengagement coping responses have been associated with poorer adjustment (e.g., Compas, Boyer, et al., 2006; Jaser et al., 2007). In order to accurately interpret and discuss the associations between brain activation and

psychosocial outcomes, it was crucial to first determine whether this pattern holds for survivors of pediatric brain tumors as well.

As expected, the results of Study 2 indicated that survivors of pediatric brain tumors performed significantly more poorly than expected based on published normative data on measures of working memory, processing speed, and overall cognitive ability. Examination of the individual scores on measures of cognitive ability again indicated quite a range of functioning within the full sample of survivors (n=17). For example, on the FSIQ, survivors' scores ranged from 72, which falls in the borderline range and corresponds to the 3rd percentile of a normative sample, to 114, which falls in the high average range and corresponds to the 82nd percentile. This reiterates the need for further examination of predictors of the magnitude of neurocognitive deficits, as the impact of diagnosis of and treatment for a pediatric brain tumor on survivors' neurocognitive functioning appears to vary considerably. Prospective longitudinal research, with pre-treatment baseline assessment of neurocognitive functioning, will provide vital information in determining the trajectory of deficits overall, and within subgroups of survivors.

When survivors' and parents' reports on measures of psychosocial and emotional functioning were compared to normative data, results indicated that scores on social competency fell significantly below the normative mean, whereas scores on measures of anxiety and depression, and social problems fell significantly above the normative mean. This is consistent with previous literature indicating that survivors experience difficulties with symptoms of internalizing disorders, including anxiety and depression, as well as deficits in social competence and social skills (e.g., Schultz et al., 2007). Examination of

the range of individual scores on these measures indicated a wide range of functioning in survivors. This suggests that, whereas some children may experience significant difficulty in areas of psychosocial functioning, others may be functioning at a level expected based on age and gender. This raises the question of whether or not certain factors may indicate which survivors will struggle and which will demonstrate resilience.

As expected, within this full sample of survivors of pediatric brain tumors, use of primary and secondary control engagement coping responses was associated with fewer emotional and behavioral problems in survivors. Specifically, survivors who reported using more primary and secondary control coping strategies were less likely to report symptoms of anxiety and depression, and less likely to endorse social problems. Similarly, when parents reported that survivors used more secondary control coping strategies, they were more likely to rate survivors as competent socially. Additionally, parents' reports of children's use of secondary control coping strategies were positively correlated with parents' ratings of children's social competence and negatively related to symptoms of anxiety and depression and social problems. In contrast, use of disengagement coping responses was associated with poorer social competence and higher rates of social problems and symptoms of anxiety and depression. Based on these findings, it was anticipated that survivors who were able to recruit greater amounts of oxygenated blood to regions underlying executive function would report fewer psychosocial and emotional problems, and would report using more engagement coping responses, as compensatory activation is thought to be an adaptive process within populations with deficits. In contrast, survivors who were less able to recruit oxygenated blood to these regions would report greater psychosocial and emotional difficulty, and

would report using more disengagement coping responses.

Within-group analyses of BOLD signal activation during the N-back task indicated that as the task difficulty of the N-back increased from the 0-back to the 2-back level, survivors recruited increasing amounts of oxygenated blood to the superior frontal gyrus (BA 8) and dorsolateral prefrontal cortex (BA 9). When task difficulty increased from the 0-back to the 3-back level, survivors recruited greater amounts of oxygenated blood to the anterior prefrontal cortex (BA 10), supramarginal gyrus (BA 40), and dorsal anterior cingulate cortex (BA 32). Each of these significantly activated regions has been consistently documented to activate during completion of the N-back task (Owen et al., 2005) and underlie functions including higher-level organization of information (BA 9), simultaneous processing of multiple cognitive tasks (BA 10), retaining temporal information regarding visual and verbal stimuli (BA 40), maintenance of visuospatial attention (BA 8), and complex problem solving (BA 32). Therefore, it appears that survivors of pediatric brain tumors activate the expected brain regions in response to a working memory task despite observed neurocognitive deficits.

The current findings are consistent with recent imaging studies with healthy and cognitively impaired adolescents. For example, Nagel and colleagues (2005) examined of BOLD signal activation patterns during a spatial working memory task in healthy adolescents, and the association between areas of brain activation and performance on measures of neurocognitive functioning. Nagel et al. found that performance on neurocognitive measures was negatively associated with brain activation. Specifically, individuals who performed better on measures of working memory, executive function, and processing speed outside of the scanner recruited less oxygenated blood to key brain

regions during fMRI including portions of the prefrontal cortex and anterior cingulate cortex (Nagel et al., 2005). These findings suggest that individuals with deficits may require increased resources in order to successfully complete tasks requiring executive function. In contrast, recent studies with adolescents with a history of heavy prenatal alcohol exposure, a condition consistently linked to neurocognitive deficits (Spadoni et al., 2009), and adolescent survivors of traumatic brain injury (Newsome et al., 2008) found that both of these groups recruited significantly more oxygenated blood to prefrontal regions in response to working memory tasks. These studies suggest that individuals with deficits may require both greater amounts of oxygenated blood to expected regions than healthy controls, as well as recruitment of a broader network of regions associated with subcomponents of executive function (Newsome et al., 2008).

The final set of analyses in this study examined the association between brain activation and measures of coping and psychosocial functioning. Recent research has suggested that coping falls within the overall set of skills associated with executive function, which are highly reliant on brain regions like the prefrontal cortex and anterior cingulate cortex (Compas, 2006; Compas et al., 2009). For example, cognitive restructuring, a secondary control coping response, requires an individual to focus attention on a stressor or problem, and simultaneously generate alternative ways to conceptualize the problem, with the goal of relieving the burden of the stressor on him or herself. A brain tumor survivor experiencing deficits in working memory may, therefore, be unable to engage in cognitive restructuring.

Within the sample of brain tumor survivors in Study 2, use of primary control coping responses was associated with increases in activation in the anterior prefrontal

cortex (BA 10) and dorsolateral prefrontal cortex (BA 9) as the difficulty of the N-back task increased. These two particular regions underlie functions such as the processing of complex, multi-level information, and keeping the information organized so that it is usable (Owen et al., 2005). Several of the specific coping responses included as primary control coping (e.g., problem solving, emotional modulation) require an individual to generate, manage and manipulate complicated bits of information, and make sense of them in a logical, organized way. These tasks rely heavily on the functions in these areas of the prefrontal cortex, and the observed pattern of activation indicates that survivors who were able to recruit increasing amounts of oxygenated blood to these areas were more likely to engage in these coping responses. Therefore, this process may be adaptive, due to the fact that use of primary control coping is associated with lower levels of psychosocial difficulty.

Similarly, survivors' use of secondary control coping responses was associated with increases in activation in the anterior prefrontal cortex (BA 10), superior frontal gyrus (BA 8), dorsal anterior cingulate cortex (BA 32), and dorsolateral prefrontal cortex (BA 9), as the difficulty of the N-back task increased. This replicates the findings of McRae et al. (2010), who examined the neurobiological underpinnings of reappraisal and distraction, two types of secondary control coping responses, and found evidence of increased activation in the prefrontal and cingulate regions. In addition to the functions associated with anterior and dorsolateral prefrontal activation described above, these regions have been linked to maintenance of attention and detecting discrepancies between a goal and one's prepotent response (Lieberman, 2007). Each of these skills better enables a person to engage in secondary control coping responses by fostering their

ability to focus their attention on a stressor or problem for a necessary period of time, and generate and examine possible alternatives with the end goal of adjusting one's reactions to a stressor. Again, recruitment of oxygenated blood to these regions appears to be an adaptive response within this sample of survivors, as use of this type of coping is associated with better outcomes.

In contrast, survivors' use of disengagement coping was negatively associated with activation in the dorsolateral prefrontal cortex (BA 9), superior frontal gyrus (BA 8), and dorsal anterior cingulate cortex (BA 32). This means that survivors who tended to disengage when faced with stress were less likely to recruit oxygenated blood to regions responsible for complex problem solving, sustained attention, and higher-level processing and organization of information. The specific coping responses included in the disengagement coping subtype (e.g., denial, avoidance) require little cognitive "effort." Survivors experiencing deficits at a neurobiological level may be unable to generate engagement coping responses reliant on these complex skills, and therefore must resort to disengagement responses. Because the temporal development of deficits and coping responses was not directly assessed, this is speculative, and worthy of future consideration.

To date, although psychosocial deficits have been well documented in survivors of pediatric brain tumors, the relationship between these deficits and underlying neurobiological processes has not been explored. In the current study, survivors' and parents' reports of symptoms of anxiety and depression were negatively associated with increases in activation in the superior frontal gyrus (BA 8), dorsolateral prefrontal cortex (BA 9), anterior prefrontal cortex (BA 10), and dorsal anterior cingulate cortex (BA 32).

This indicates that survivors who were better able to recruit oxygenated blood to regions associated with complex problem solving, sustained attention, and higher-level executive function were less likely to be experiencing symptoms of internalizing disorders. Overall, this pattern of associations indicates that activation in these brain regions is adaptive for survivors of pediatric brain tumors.

Within this sample, brain tumor survivors who were rated as having higher social competence were more likely to recruit oxygenated blood to the anterior prefrontal cortex (BA 10). In contrast, survivors' and parents' reports of social problems were negatively associated with increases in activation in the superior frontal gyrus (BA 8), dorsolateral prefrontal cortex (BA 9), anterior prefrontal cortex (BA 10), and dorsal anterior cingulate cortex (BA 32). This makes intuitive sense, as individuals higher in social competence likely experience fewer social problems. Navigation of the social world requires an individual to simultaneously attend to and process high volumes of social information, including verbal and nonverbal social cues, generate potential responses, and anticipate the consequences of these responses (Crick & Dodge, 1994). Research has shown that survivors show significant impairment on tasks that assess these aspects of social functioning (e.g., Bonner et al., 2008), and this pattern of brain activation suggests that individuals who are unable to successfully recruit oxygenated blood to these areas linked to social information processing via their role in regulation of attention and working memory, are more likely to report difficulties socially.

These findings are consistent with research with other clinical populations. For example, Mah, Arnold, and Grafman (2004) examined deficits in social domains in individuals with a history of insult to the orbitofrontal cortex (including the anterior

prefrontal cortex), dorsolateral prefrontal cortex, and anterior cingulate cortex. Their findings indicated that those with damage to the orbitofrontal cortex demonstrated deficits in social perception, whereas individuals with damage to the dorsolateral prefrontal cortex demonstrated deficits in the use of social cues to make informed judgments, as well as impaired insight into their own deficits. This has an impact on one's ability accurately interpret the social environment and respond in social situations. The measures of social functioning used in the current study do not separate aspects of social perception from social skills onto different subscales, so additional research examining more specific aspects of social functioning as related to neurobiological processes may be helpful in further understanding the origin of survivors' social problems.

Research has also examined differences in psychosocial outcomes based on aspects of survivors' treatment. First, there is evidence that broad characteristics of treatment (e.g., surgery vs. surgery+radiation) and more specific factors like treatment side effects (e.g., posterior fossa syndrome, hydrocephalus) may be important predictors of outcome (e.g., Wolfe-Christensen, Mullins, Scott, & McNall-Knapp, 2007). Second, some studies have found age at diagnosis to be related to social outcomes; however, whereas some of these implicate older age at diagnosis as predictive of poor outcomes (e.g., Aarsen et al., 2006), others suggest younger age at diagnosis is a risk factor (e.g., Foley et al., 2000). Third, time since diagnosis has emerged a consistent predictor of later social deficits, with longer time since diagnosis predictive of greater deficits (Schulte & Barrera, 2010).

Tumor characteristics and histology, patient characteristics, and characteristics of

the treatment received all may play a role in the nature and extent of deficits (e.g., Glauser & Packer, 1991; Mulhern et al., 1992; Nathan, Patel, Dilley, Goldsby, Harvey, Jacobsen, et al., 2007). Consideration of these moderating factors has been limited to individual studies, and synthesis of this information has been complicated by the variety of approaches to recording and presenting demographic, diagnostic and treatment information. A meta-analysis to examine the potential risk factors for later neurocognitive deficits in survivors of pediatric brain tumors is currently in preparation, and suggests that patient age and radiation dosage will be important to examine in future research (Robinson et al., 2011).

There are several strengths to the current study that provide unique contributions to this area of research. This is the first known study to use fMRI to examine the substrates of neurocognitive deficits in survivors of pediatric brain tumors. Further, this study presented the first comparison of differences in patterns of brain activation during this working memory task between childhood brain tumor survivors and healthy controls. This contributes to our understanding of the neurobiological processes underlying executive function abilities in survivors. Greater understanding of these processes provides a starting point for examination of the association between patterns of activation and other areas of survivors' functioning. Another strength of the current study was the selection of a healthy control sample, matched for age and gender, against whom to compare measures of neurocognitive function and BOLD signal activation. This allowed for the discussion of patterns of activation in survivors not only from one N-back level to another, but also relative to a sample of typically-developing children. This is the first study to examine the relationship between neurocognitive and psychosocial functioning,

and coping responses, within this population. This study also relied on multiple methodological approaches, including neurocognitive assessment using standardized and norm-referenced measures, empirically-validated questionnaires, a well-established verbal working memory task conducted during functional neuroimaging, and changes in BOLD signal activation during increasingly difficult levels of the verbal working memory task.

Despite these strengths, several limitations need to be considered while interpreting these results. In our examination of between-group differences, our sample size was limited to 7 children in each group. Analyses of imaging data were corrected for multiple comparisons, with the goal of reducing the likelihood of Type I error, but this limited sample nonetheless reduced the ability to detect smaller but potentially meaningful differences in activation between survivors and healthy controls. In order to detect between-group differences on cognitive measures using *t*-tests, differences needed to be quite large. Therefore, effect sizes were provided to further explore potentially meaningful effects in the absence of statistical significance. A larger number of participants in each group, matched for age and gender, would be helpful for improving confidence in the reliability of the detected effects. Further, although survivors and healthy controls were matched well based on age, gender, race, and socioeconomic status, healthy control participants' scores on the WISC-IV were in the high-average range for processing speed and full scale IQ. It is possible that results of comparisons against this group of healthy children may not replicate with a sample of children whose scores corresponded more exactly to normative data. Finally, although the majority of the group differences in brain activation replicate findings of previous research, differences

detected in postcentral gyrus (BA 2) were unanticipated. Further research exploring the significance of this region in completion of a working memory in healthy children is warranted.

Several avenues of further research would contribute greatly to our understanding of the associations explored in this study. First, additional examination of the similarities and differences in neurobiological processes underlying executive and psychosocial function, and coping, in survivors relative to healthy children is necessary due to the limited sample size available in this study and the associated limitations on our ability to detect smaller but potentially clinically significant effects. Second, considerable research has indicated that the emergence of neurocognitive and psychosocial functioning deficits in survivors is reliant on various qualities of the survivors and their diagnosis and treatment. Future analyses exploring differences in these associations within a larger sample of survivors would allow for the consideration of subgroups identified by demographic, diagnostic, or treatment-related variables and contribute to the broader understanding of moderators of risk and resilience in this population. Third, the temporal development of difficulties in executive and psychosocial function in survivors of pediatric brain tumor has yet to be determined. Although some longitudinal studies document the emergence of neurocognitive deficits in survivors (e.g., Copeland, deMoor, Moore, & Ater, 1999; Stargatt, Rosenfeld, Maixner, & Ashley, 2007), methodological limitations dampen our ability to draw conclusions about these processes. Finally, a better understanding of the underlying neurobiological processes associated with executive function, psychosocial functioning, and coping in survivors will provide useful information for the development of intervention strategies aimed at one or more of these

domains.

In conclusion, this study replicates prior research documenting neurocognitive and psychosocial deficits in survivors of pediatric brain tumors, and extends this area of research by examining related neurobiological processes and their association with these areas of functioning. These findings contribute considerably to our understanding of these difficulties in this important clinical population, and provide a foundation for research that is directed at exploring the nuances of these associations and their plasticity, with the end goal of improving the post-treatment experience of survivors of pediatric brain tumors.

REFERENCES

Aarsen, F. K., Paquier, P. F., Reddingius, R. E., Streng, I. C., Arts, W. F. M., Evera-Preesman, M., & Catsman-Berrevoets, C. E. (2006). Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer, 106*, 396-402.

Achenbach, T. M., & Rescorla, L. A. (1991). *Manual for the Child Behavior Checklist/14-18 and 1991 profile*. Burlington: Department of Psychiatry, University of Vermont.

Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology, 11*, 231-239.

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review, 16*, 17-42.

Amodio, D. M., & Frith, C. D., (2005). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews: Neuroscience, 7*, 268-277.

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography. *Physiological Science, 7*, 25-31.

Barch, D. M., Sheline, Y. I., Csernansky, J. G., & Snyder, A. Z. (2003). Working memory and prefrontal cortex dysfunction: Specificity to schizophrenia compared with major depression. *Biological Psychiatry, 53*, 376-384.

Bonner, M. J., Hardy, K. K., Willard, V. W., Anthony, K. K., Hood, M., & Gururangan, S. (2008). Social functioning and facial expression recognition in survivors of pediatric brain tumors. *Journal of Pediatric Psychology, 33*, 1142-1152.

Boydell, K. M., Stasiulis, E., Greenberg, M., Greenberg, C., & Spiegler, B. (2008). I'll show them: The social construction of (in)competence in survivors of childhood brain tumors. *Journal of Pediatric Oncology Nursing, 25*, 164-174.

Campbell, L. K., Scaduto, M., Sharp, W., Dufton, L., Van Slyke, D., Whitlock, J. A., … Compas, B. E. (2007). A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. *Pediatric Blood and Cancer, 49*, 65-73.

Campbell, L. K., Scaduto, M., Van Slyke, D., Niarhos, F., Whitlock, J. A., & Compas, B. E. (2009). Executive function, coping, and behavior in survivors of childhood acute lymphocytic leukemia. *Journal of Pediatric Psychology, 34*, 317-327.

Carey, M. E., Barakat, L. P., Foley, B., Gyato, K., & Phillips, P. C. (2001). Neuropsychological functioning and social functioning of survivors of pediatric brain tumors: Evidence of nonverbal learning disability. *Child Neuropsychology, 7,* 265-272.

Carpentieri, S. C., Mulhern, R. K., Douglas, S., Hanna, S., & Fairclough, D. (1993). Behavioral resiliency among children surviving brain tumors: A longitudinal study. *Journal of Clinical Child Psychology, 22,* 236-246.

CBTRUS (2011). Statistical Report: Primary Brain Tumors in the United States, 2004-2007. Published by the Central Brain Tumor Registry of the United States.

Cohen, J. (1988). *Statistical power analysis for behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112,* 155-159.

Collette, F., Hogge, M., Salmon, E., & Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience, 139,* 209-221.

Compas, B. E. (2006). Psychobiological processes of stress and coping: Implications for resilience in children and adolescents. *Annals of the New York Academy of Sciences, 1094,* 226-234.

Compas, B. E., Beckjord, E., Agocha, B., Sherman, M. L., Langrock, A., Grossman, C. I., … Luecken, L. (2006). Measurement of coping and stress responses in women with breast cancer. *Psycho-Oncology, 15,* 1038-1054.

Compas, B. E., & Boyer, M. C. (2001). Coping and attention: Implications for child health and pediatric conditions. *Journal of Developmental and Behavioral Pediatrics, 22,* 323-333.

Compas, B. E., Boyer, M. C., Stanger, C., Colletti, R. B., Thomsen, A. H., Dufton, L. M., & Cole, D. A. (2006). Latent variable analysis of coping, anxiety/depression, and somatic symptoms in adolescents with chronic pain. *Journal of Consulting and Clinical Psychology, 76,* 1132-1142.

Compas, B. E., Campbell, L. K., Robinson, K. E., & Rodriguez, E. (2009). Coping and memory: Automatic and controlled processes in response to stress. In J. Quas & R. Fivush (Eds.), *Emotion and memory in development: Biological, cognitive, and social considerations* (pp. 121-141). New York: Oxford University Press.

Compas, B. E., Connor-Smith, J. K., Saltzman, H., Thomsen, A. H., & Wadsworth, M. E. (2001). Coping with stress during childhood and adolescence: Progress, problems, and potential in theory and research. *Psychological Bulletin, 127,* 87-

127.

Connor-Smith, J. K., Compas, B. E., Wadsworth, M. E., Thomsen, A., & Saltzman, H. (2000). Responses to stress in adolescence: Measurement of coping and involuntary stress responses. *Journal of Consulting and Clinical Psychology, 68,* 976-992.

Copeland, D. R., deMoor, C., Moore, B. D., & Ater, J. L. (1999). Neurocognitive development of children after a cerebellar tumor in infancy: A longitudinal study. *Journal of Clinical Oncology, 17,* 3476-3486.

Crick, N. R., & Dodge, K. A. (1994). A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychological Bulletin, 115,* 74-101.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neuroscience, 23,* 475-483.

Dykes, R. W. (1978). Anatomy and physiology of somatic sensory cortical regions. *Progress in Neurobiology, 10,* 33-88.

Foley, B., Barakat, L. P., Herman-Liu, A., Radcliffe, J., & Molloy, P. (2000). The impact of childhood hypothalamic/chiasmatic brain tumors on child adjustment and family functioning. *Children's Health Care, 29,* 209-223.

Fossen, A., Abrahamsen, T. G., & Storm-Mathisen, I. (1998). Psychological outcome in children treated for brain tumor. *Pediatric Hematology and Oncology, 15,* 479-488.

Fuemmeler, B. F., Elkin, T. D., & Mullins, L. L. (2002). Survivors of childhood brain tumors: Behavioral, emotional, and social adjustment. *Clinical Psychology Review, 22,* 547-585.

Fuemmeler, B. F., Mullins, L. L., Van Pelt, J., Carpentier, M. Y., & Parkhurst, J. (2005). Posttraumatic stress symptoms and distress among parents of children with cancer. *Children's Health Care, 34,* 289-303.

Gerhardt, C. A., Rutherford, C. G., Fairclough, D. L., Kupst, M. J., Patenaude, A. F., & Vannatta, K. (2008, April 10-12). *Emotional and behavioral functioning of children surviving brain tumor and comparison peers.* Paper presented at the National Conference on Child Health Psychology, Miami, FL.

Glauser, T. A., & Packer, R. J. (1991). Cognitive deficits in long-term survivors of childhood brain tumors. *Child's Nervous System, 7,* 2-12.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., …

Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, 101,* 8174-8179.

Gottardo, N. G., & Gajjar, A. (2008). Chemotherapy for malignant brain tumors of childhood. *Journal of Child Neurology, 23,* 1149-1159.

Hardy, K. K., Willard, V. W., Watral, M. A., & Bonner, M. J. (2010). Perceived social competency in children with brain tumors: Comparison between children on and off therapy. *Journal of Pediatric Oncology Nursing, 27,* 156-163.

Hirsch, J. F., Renier, D., Czernichow, P., Benveniste, L., & Pierre-Kahn, A. (1979). Medulloblastoma in childhood: Survival and functional results. *Acta Neurochirurgica, 48,* 1-15.

Hocking, M. C., Barnes, M., Shaw, C., Lochman, J. E., Madan-Swain, A., & Saeed, S. (2011). Executive function and attention regulation as predictors of coping success in youth with functional abdominal pain. *Journal of Pediatric Psychology, 36,* 64-73.

Holmquist, L. A., & Scott, J. (2002). Treatment, age, and time-related predictors of behavioral outcome in pediatric brain tumor survivors. *Journal of Clinical Psychology in Medical Settings, 9,* 315-321.

Hoppe-Hirsch, E., Renier, D., Lellouch-Tubiana, A., Sainte-Rose, C., Pierre-Kahn, A., & Hirsch, J. F. (1990). Medulloblastoma in childhood: Progressive intellectual deterioration. *Child's Nervous System, 6,* 60-65.

Jaser, S. S., Champion, J. E., Reeslund, K. L., Keller, G., Merchant, M. J., Benson, M., & Compas, B. E. (2007). Cross-situational coping with peer and family stressors in adolescent offspring of depressed parents. *Journal of Adolescence, 30,* 917-932.

Jonides, J., Schumacher, E. H., Smith, E. E., Koeppe, R. A., Awh, E., Reuter-Lorenz, P. A., ... Willis, C. R. (1998). The role of the parietal cortex in verbal working memory. *Journal of Neuroscience, 18,* 5026-5034.

Kiehl, K. A., Liddle, P. F., & Hopfinger, J. B. (2000). Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology, 37,* 216-223.

Kwon, H., Reiss, A. L., & Menon, V. (2002). Neural basis of protracted developmental changes in visuo-spatial working memory. *Proceedings of the National Academy of Sciences, 99,* 13336-13341.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., ... Fox, P. T. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping, 10,* 120-131.

Lemerise, E. A., & Arsenio, W. F. (2000). An integrated model of emotion processes and cognition in social information processing. *Child Development, 71*, 107-118.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological Assessment*. New York, NY: Oxford University Press.

Lieberman, M. D. (2007). Social cognitive neuroscience: A review of core processes. *Annual Review of Psychology, 58*, 259-289.

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Development, 75*, 1357-1372.

Luna, B., & Sweeney, J. A. (2004). The emergence of collaborative brain function: fMRI studies of the development of response inhibition. *Annals of the New York Academy of Science, 1021*, 296-309.

Mabbott, D. J., Spiegler, B. J., Greenberg, M. L., Rutka, J. T., Hyder, D. J., & Bouffet, E. (2005). Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *Journal of Clinical Oncology, 23*, 2256-2263.

Mah, L. W., Arnold, M. C., & Grafman, J. (2004). Impairment of social perception associated with lesions of the prefrontal cortex. *American Journal of Psychiatry, 161*, 1247-1255.

McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., … Yanofsky, N. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology, 53*, 1300-1308.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D. E., Gross, J. J., & Ochsner, K. N. (2010). The neural bases of distraction and reappraisal. *Journal of Cognitive Neuroscience, 22*, 248-262.

Meeske, K., Katz, E. R., Palmer, S. N., Burwinkle, T., & Varni, J. W. (2004). Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer, 101*, 2116-2125.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping, 12*, 131-143.

Merchant, T. E., Pollack, I. F., & Loeffler, J. S. (2010). Brain tumors across the age spectrum: Biology, therapy, and late effects. *Seminars in Radiation Oncology,*

20, 58-66.

Mulhern, R. K., & Butler, R. W. (2004). Neurocognitive sequelae of childhood cancers and their treatment. *Pediatric Rehabilitation, 7*, 1-14.

Mulhern, R. K., Carpentieri, S., Shema, S., Stone, P., & Fairclough, D. (1993). Factors associated with social and behavioral problems among children recently diagnosed with brain tumor. *Journal of Pediatric Psychology, 18*, 339-350.

Mulhern, R. K., Hancock, J., Fairclough, D., & Kun, L. K. (1992). Neuropsychological status of children treated for brain tumors: A critical review and integrative analysis. *Medical and Pediatric Oncology, 20*, 181-191.

Mulhern, R. K., White, H. A., Glass, J. O., Kun, L. E., Leigh, L., Thompson, S. J., & Reddick, W. E. (2004). Attentional functioning and white matter integrity among survivors of malignant brain tumors of childhood. *Journal of the International Neuropsychological Society, 10*, 180-189.

Nagel, B. J., Barlett, V. C., Schweinsburg, A. D., & Tapert, S. F. (2005). Neuropsychological predictors of BOLD response during a spatial working memory task in adolescents: What can performance tell us about fMRI response patterns? *Journal of Clinical and Experimental Neuropsychology, 27*, 823-839.

Nassau, J. H., & Drotar, D. (1997). Social competence among children with central nervous system-related chronic health conditions: A review. *Journal of Pediatric Psychology, 22*, 771-793.

Nathan, P. C., Patel, S. K., Dilley, K., Goldsby, R., Harvey, J., Jacobsen, C., … Armstrong, F. D. (2007). Guidelines for identification of, advocacy for, and interventions in neurocognitive problems in survivors of childhood cancer: A report from the Children's Oncology Group. *Archives of Pediatric and Adolescent Medicine, 161*, 798-806.

National Cancer Institute. (2008, April). Childhood cerebellar astrocytoma treatment (PDQ®). Retrieved July 28, 2009, from http://www.cancer.gov/cancertopics/pdq/treatment/child-cerebellar-astrocytoma.

Nelson, C. A., Monk, C. S., Lin, J., Carver, L. J., Thomas, K. M., & Truwit, C. L. (2000). Functional neuroanatomy of spatial working memory in children. *Developmental Psychology, 36*, 109-116.

Ness, K. K., & Gurney, J. G. (2007). Adverse late effects of childhood cancer and its treatment on health and performance. *Annual Review of Public Health, 28*, 279-302.

Newsome, M. R., Steinberg, J. L., Scheibel, R. S., Troyanskaya, M., Chu, Z., Hanten, G.,

…Levin, H. S. (2008). Effects of traumatic brain injury on working memory-related brain activation in adolescents. *Neuropsychology, 22*, 419-425.

Owen, A. M., Evans, A. C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emossion tomography study. *Cerebral Cortex, 6*, 31-38.

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping, 25*, 46-59.

Packer, R. J., Meadows, A. T., Rorke, L. B., Goldwein, J. L., & D'Angio, G. (1987). Long-term sequelae of cancer treatment on central nervous system in childhood. *Medical and Pediatric Oncology, 15*, 241-253.

Palmer, S. N., Meeske, K. A., Katz, E. R., Burwinkle, T. M., & Varni, J. W. (2007). The PedsQL Brain Tumor Module: Initial reliability and validity. *Pediatric Blood and Cancer, 49*, 287-293.

Panigrahy, A., & Bluml, S. (2009). Neuroimaging of pediatric brain tumors: From basic to advanced magnetic resonance imaging (MRI). *Journal of Child Neurology, 24*, 1343-1365.

Partap, S., & Fisher, P. G. (2007). Update on new treatments and developments in childhood brain tumors. *Current Opinions in Pediatrics, 19*, 670-674.

Pause, M., Kunesch, E., Binkofski, F., & Freund, H. J. (1989). Sensorimotor disturbances in patients with lesions of the parietal cortex. *Brain, 112*, 1599-1625.

Poggi, G., Liscio, M., Adduci, A., Galbiati, S., Massimino, M., Sommovigo, M., … Castelli, E. (2005). Psychological and adjustment problems due to acquired brain lesions in childhood: A comparison between post-traumatic patients and brain tumor survivors. *Brain Injury, 19*, 777-785.

Radcliffe, J., Bennet, D., Kazak, A. E., Foley, B., & Phillips, P. C. (1996). Adjustment in childhood brain tumor survival: Child, mother, and teacher report. *Journal of Pediatric Psychology, 21*, 529-539.

Rama, P., Martinkauppi, S., Linnankoski, I., Koivisto, J., Aronen, H., & Carlson, S. (2001). Working memory of identification of emotional vocal expressions: An fMRI study. *Neuroimage, 13*, 1090-1101.

Rey-Casserly, C., & Parsons, S. K. (2006). *Emotional adjustment, leadership, and depressive symptoms among adolescent survivors of brain tumors*. Psychosocial and Neurocognitive Consequences of Childhood Cancer: A Symposium in

Tribute to Raymond K. Mulhern; 2006; Memphis, TN.

Robinson, K. E., Fraley, C. E., Thigpen, J. E., Andreotti, C. F., Hipp, D. W., Bettis, A., et al. (2011). *A Quantitative Meta-Analysis of the Neurocognitive Late Effects in Children with Posterior Fossa Brain Tumors*. Manuscript in preparation.

Robinson, K. E., Kuttesch, J. F., Champion, J. E., Andreotti, C. F., Hipp, D. W., Bettis, A., … Compas, B. E. (2010). A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatric Blood and Cancer, 55*, 525-531.

Robinson, K. E., Livesay, K. L., Campbell, L. K., Scaduto, M., Cannistraci, C. J., Anderson, A. W., … Compas, B. E. (2010). Working memory in survivors of acute lymphocytic leukemia: Functional neuroimaging analyses. *Pediatric Blood and Cancer, 54*, 585-590.

Rosoff, P. M. (2006). The two-edged sword of curing childhood cancer. *New England Journal of Medicine, 355*, 1522-1523.

St. Jude Children's Research Hospital. (2009). Disease information: Optic pathway tumors. Retrieved July 28, 2009, from http://www.stjude.org/stjude.

Satpute, A. B., & Lieberman, M. D. (2006). Integrating automatic and controlled processes into neurocognitive models of social cognition. *Brain Research, 1079*, 86-97.

Schulte, F., & Barrera, M. (2010). Social competence in childhood brain tumor survivors: A comprehensive review. *Supportive Care in Cancer, 18*, 1499-1513.

Schultz, K. A., Ness, K. K., Whitton, J., Recklitis, C., Zebrack, B., Robison, L. L., … Mertens, A. C. (2007). Behavioral and social outcomes in adolescent survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 25*, 3649-3656.

Seaver, E., Geyer, R., Sulzbacher, S., Warner, M., Batzel, L., Milstein, J., & Berger, M. (1994). Psychosocial adjustment in long-term survivors of childhood medulloblastoma and ependymoma treated with craniospinal irradiation. *Pediatric Neurosurgery, 20*, 248-253.

Sklar, C. A. (2002), Childhood brain tumors. *Journal of Pediatric Endocrinology and Metabolism, 15*, 669-673.

Spadoni, A. D., Bazinet, A. D., Fryer, S. L., Tapert, S. F., Mattson, S. N., & Riley, E. P. (2009). BOLD response during spatial working memory in youth with heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 33*, 2067-2076.

Stargatt, R., Rosenfeld, J. V., Maixner, W., & Ashley, D. (2007). Multiple factors contribute to neuropsychological outcome in children with posterior fossa tumors. *Developmental Neuropsychology, 32*, 729-748.

Sweet, L. H., Rao, S. M., Primeau, M., Durgerian, S., & Cohen, R. A. (2006). Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. *Human Brain Mapping, 27*, 28-36.

Tamnes, C. K., Ostby, Y., Walhovd, K. B., Westlye, L. T., Due-Tonnessen, P., & Fjell, A. M. (2010). Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness. *Neuropsychologia, 48*, 2496-2508.

Thomas, K. M., King, S. W., Franzen, P. L., Welsh, T. F., Berkowitz, A. L., Noll, D. C., … Casey, B. J. (1999). A developmental functional MRI study of spatial working memory. *Neuroimage, 10*, 327-338.

Turner, C. D., Rey-Casserly, C., Liptak, C. C., & Chordas, C. (2009). Late effects of therapy for pediatric brain tumor survivors. *Journal of Child Neurology, 24*, 1455-1463.

Ullruch, N. J. (2009). Neurologic sequelae of brain tumors in children. *Journal of Child Neurology, 24*, 1446-1454.

Vannatta, K., Gartstein, M. A., Short, A., & Noll, R. B. (1998). A controlled study of peer relationships of children surviving brain tumors: Teacher, peer, and self ratings. *Journal of Pediatric Psychology, 23*, 279-287.

Wadsworth, M. E., Rieckmann, T., Benson, M. A., & Compas, B. E. (2004). Coping and responses to stress in Navajo adolescents: Psychometric properties of the Responses to Stress Questionnaire. *Journal of Community Psychology, 32*, 391-411.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children – Fourth Edition Technical and Interpretive Manual.* San Antonio, TX: The Psychological Corporation.

Wolfe-Christensen, C., Mullins, L. L., Scott, J. G., & McNall-Knapp, R. Y. (2007). Persistent psychological problems in children who develop posterior fossa syndrome after medulloblastoma resection. *Pediatric Blood and Cancer, 49*, 723-726.

Yeates, K. O., Bigler, E. D., Dennis, M., Gerhardt, C. A., Rubin, K. H., Stancin, T., … Vannatta, K. (2007). Social outcomes in childhood brain disorder: A heuristic

integration of social neuroscience and developmental psychology. *Psychological Bulletin, 133*, 535-556.

Zebrack, B. J., & Chesler, M. (2001). Health-related worries, self image, and life outlooks of long term survivors of childhood cancer. *Health and Social Work, 26*, 245-256.

Zou, P., Mulhern, R. K., Butler, R. W., Li, C., Langston, J. W., & Ogg, R. J. (2005). BOLD response to visual stimulation in survivors of childhood cancer. *Neuroimage, 24*, 61-69.